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THE LIFE-SAVING POWER OF "SAFE" UNIVERSAL DONOR BLOOD IN EXSANGUINATING HEMORRHAGE.

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In 1935, Marriott and Kekwick[3a,b] pointed out that the routine procedure of giving 500 cc. of blood at each transfusion to adults was often inadequate in severe anemias and in bleeding cases. They have performed 194 transfusions of citrated blood by the drip method, administering an average of between 2 and 4 liters of blood per case. One of their patients received as much as 5650 cc. of blood within a 48-hour period. These workers did not restrict themselves to the use of donors of the homologous group but also used donors of other groups according to the universal donor principle. They apparently relied on the slow rate of infusion which allowed time for the body to dispose of the foreign isoagglutinins.

The use of universal donor blood for patients not belonging to Group O is usually regarded as unsafe when the isoagglutinins in the donor's serum are of high titer.[2] Though the slow infusion of such blood is probably harmless, if the blood is injected rapidly over a short period of time, particularly to a severely anemic patient, hemolysis of the patient's own blood cells could conceivably occur. Indeed, a number of reports of hemolytic reactions following the use of universal donor's blood have appeared, which have been

attributed to this mechanism.[1,4] Witebsky, Klendshoj and Swanson[6,7] have advocated the routine addition to the citrated Group O donor's blood of a solution of purified A and B substances in order to neutralize the isoagglutinins and make the blood safe for patients of all groups.

Case Report. A man, aged 65, while under observation at the hospital for peptic ulcer, suddenly went into shock; his blood pressure dropped to 50/30, his pulse being almost imperceptible, his skin cold and clammy, and he passed a large amount of blood by rectum.

The patient was typed as Group AB, and transfusions totaling 1100 cc. of citrated blood from two compatible AB donors were given. Within 5 hours the patient reacted and his blood pressure rose to 108/76. During the night, however, he had another large hemorrhage and in the morning was again in shock. A transfusion was started at once. Operation, by Dr. Louis Berger, revealed a penetrating duodenal ulcer at the base of which was the eroded and bleeding pancreatico-duodenal artery. The bleeding from the eroded vessel was controlled and a subtotal gastrectomy was performed.

During the procedure the transfusion of citrated blood was continued, the blood being allowed to run in rather rapidly. When 2000 cc. of blood, in addition to the 1100 cc. given on the previous day, had been transfused, no more Group AB donors could be obtained. Accordingly, additional blood was taken from Group O donors, 10 cc. of Witebsky's solution of purified Group A and B substance* being added to each 500 cc. of blood. In this manner 2000 cc. of universal donor blood were transfused. The patient responded to the transfusions only after the bleeding vessel had been located and ligated by Dr. Berger. By the time the procedure was completed, the patient had received a total of more than 5000 cc. of blood.

Immediately after the operation, the patient's blood pressure was 150/90, pulse rate 100 and of good quality; his skin was dry and warm and his general condition good. He improved slowly after the operation but in general his convalescence was uneventful.

Comment. As a precaution the isoagglutinins in the blood from 4 Group O donors, used for transfusing a Group AB patient, were neutralized by adding a solution of purified A and B substances as recommended by Witebsky, Klendshoj and Swanson. Whether or not harm would have resulted if this procedure had not been followed cannot be determined, but the efficiency of the group substances in neutralizing the isoagglutinins has been demonstrated by titration tests *in vitro*, (cf. Table 1) which indicate at least that this procedure eliminates a theoretical danger. The group substances have been used in transfusions by Witebsky *et al.*, in more than 100 cases, and by the present authors in about 20 cases without the occurrence of any untoward reaction.

Grouping tests on our patient's blood after the transfusion showed it to consist of a mixture of approximately equal parts of Group O and Group AB blood, demonstrating that the blood of the Group O donors as well as that of the Group AB donors remained in the patient's circulation.

The fact that the patient's hemoglobin after the operation was

* The authors are indebted to Dr. E. Witebsky and to the Eli Lilly Company for their courtesy in providing this material.

only 88% while on admission it had been 100%, and this despite the transfusion of more than 5 liters of blood, indicates that he lost at least as much blood as he received. In fact, the patient must have been almost completely exsanguinated, and there can be no doubt that without the transfusions he could not have survived the operative procedure.

TABLE 1.—EFFECT OF ADDITION TO GROUP O DONOR'S CITRATED BLOOD OF A SOLUTION OF A AND B GROUP SUBSTANCES ON THE TITERS OF THE ISOAGGLUTININS IN THE PLASMA.

Donor's plasma.	Tested against cells.	Dilutions of plasma.							
		Undil.	1.2.	1:4.	1:8.	1:16.	1:32.	1:64.	1:128.
Before addition of group substance	A_1	++	+++	+++	+++	++	+	tr.	−
	B	++	++	++	++	+	tr.	−	
	Rabbit	hem.	+++	++	++	++	+	tr.	−
After addition of group substance	A_1	±	tr.	−	−				
	B	−	−	−	−				
	Rabbit	+++	++	++	+±	±	−	−	

One drop each of plasma or plasma dilution and test cells (2% suspension in terms of blood sediment) were mixed in small test tubes. Readings were taken after 1 hour.

Note that while the anti-A and anti-B isoagglutinins are neutralized by the group substances, the titer of the agglutinins for rabbit cells is only slightly reduced. This demonstrates the specificity of the reactions.

It should be noted that the transfusion of plasma alone in our case would undoubtedly have been inadequate to maintain life on account of the vast amount of blood lost. While in smaller hemorrhages the loss of red cells is not serious and satisfactory results can be obtained by merely restoring the blood volume with transfusion of plasma, in larger hemorrhages replacement of at least part of the lost erythrocytes is essential. In emergencies when whole blood is not available or is available only in small amounts, plasma is of great value and certainly far superior to glucose and saline infusions; but if the hemorrhage continues, it is recommended that at least one transfusion of whole blood be given for every 2 or 3 transfusions of plasma. In this connection the transfusion of outdated bank blood, *e. g.*, blood stored in citrate without glucose for more than 2 weeks, would have resulted in only temporary benefit to our patient since the erythrocytes of such blood are rapidly broken down and eliminated from the circulation within a few hours or days.[5]

Summary. A patient almost completely exsanguinated by bleeding from a duodenal ulcer, was operated on and the vessel ligated. Preoperatively and during the operation (all within a period of less than 24 hours) the patient, who belongs to Group AB, received transfusions totaling well over 5000 cc. of blood from 10 blood donors. Six of the donors used belonged to Group AB, 4 to Group O. To the blood of the latter a purified solution of group substances was added to neutralize the isoagglutinins. Clinical recovery followed in a situation in which customary transfusion procedures would undoubtedly have been inadequate.

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GELATIN AS A SUBSTITUTE FOR BLOOD AFTER EXPERIMENTAL HEMORRHAGE.*

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The possibility that solutions of gelatin might be used to restore the volume of circulating fluid, has occurred to a number of investigators.[4,9,11] Recently, increased interest in blood substitutes has led to a more detailed study[10] of certain types of gelatin. Transfusions of solutions of isinglass, made from the swim-bladders of fish, have been shown to insure the survival of dogs after massive hemorrhage which otherwise would be likely to end fatally.[9] Gelatin made from calfskin has been shown to be even more effective than isinglass for this purpose, to remain in the circulation in detectable concentration for at least 24 hours, and to be non-toxic and non-antigenic for dogs and rabbits.[10] Since gelatin, even of the highest grade, is not a pure substance, but a mixture, it is subject to considerable variation when prepared in different plants, and even when prepared in the same plant at different times. It seemed desirable, therefore, to repeat some of the older experiments, using a specially prepared gelatin. The gelatin selected was prepared by hydrolysis of alkali-treated bone collagen, and was supplied as calcium gelatinate.‡ The danger of contamination with pathogenic spores, as suggested by some workers,[9] is probably less with gelatin prepared from bone than with gelatin prepared from hides.

It is well known that even crystalloidal injections may temporarily restore the volume of the circulation[1] and, by permitting an animal

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† Supported in part by a grant from the Abbott Laboratories, North Chicago, Ill.
‡ The gelatin was furnished by The Knox Gelatine Company, Johnstown, N. Y.

to mobilize its plasma proteins, allow survival of an otherwise fatal hemorrhage. For this reason, the observation that the injection of a solution causes animals to survive massive hemorrhage offers no basis for judging its relative effectiveness as a blood substitute. The experiments reported here were planned to provide a *direct* comparison between gelatin and a crystalloidal solution, and between gelatin and defibrinated blood.

Materials, Methods, and Results. Four samples, obtained at different times, of each of two types of gelatin, were studied. The average molecular weight of Type 1 was reported as being higher than that of Type 2. An 8% solution of No. 1 and a 10% solution of No. 2, in 0.9% sodium chloride, were found to be sufficiently fluid, when warmed to body temperature, to pass through a 21-gauge needle. These solutions were autoclaved at 15 pounds pressure for 20 minutes, and stored in sterile containers at 4° C. All solutions were cultured aërobically and anaërobically. No growth has been obtained in any of the 35 solutions which have been prepared during the course of this study. Solution 1, after autoclaving, had specific gravity 1.2, pH 5.93, and colloidal osmotic pressure (in collodion bag against 0.9% sodium chloride) 8.5 mm. Hg. Solution 2 had specific gravity 1.25, pH 6.0, and colloidal osmotic pressure 14.5 mm. Hg.

A preliminary study of the toxicity of the autocalved gelatin solutions was done on a series of 7 dogs. In none of these was a change in arterial pressure or respiration obtained on injection of as much as 20 cc./kg. of either type of gelatin, at an injection rate of approximately 3 cc./kg./min. The effect of excessively large doses (up to 90 cc./kg.) was studied by withdrawing blood in equal volume as the gelatin solution was injected. Even in these doses no depressor agents could be demonstrated. Confirmatory data were obtained in the course of the studies reported below, in which arterial pressure lowered by previous hemorrhage underwent steady elevation to approximately its prehemorrhage level as gelatin solution was injected. The latter studies have been extended to include a total of 8 samples of gelatin and a total of 45 dogs, without obtaining evidence for toxicity in any case.

Antigenicity of the autoclaved solutions of gelatin was studied in 2 dogs. After receiving 40 cc./kg. of gelatin solution in replacement of blood lost by hemorrhage, they were permitted to recover. Nine and 11 weeks later, respectively, they were etherized and injected with 40 cc./kg. of the original solution, without effect on arterial pressure or respiration.

Postmortem examination was done on all the animals used in the toxicity studies, including the 2 animals which were permitted to survive. In no case was evidence of thrombosis, hemolysis, embolism, or capillary damage found. Necropsies were also done on some of the animals used in other portions of the study, without revealing pathologic changes.

Since neither type of gelatin appeared to be toxic for the dog, and since the data offer no clear-cut evidence that they differ in effectiveness as circulating fluid, the data on the two types are treated collectively in the following.

A comparison of the solutions studied (8 or 10% gelatin in 0.9% NaCl, 5% glucose in 0.9% NaCl, and defibrinated blood) was obtained by determining, in dogs under ether anesthesia: (*a*) the percentage restoration of carotid arterial pressure (Hg manometer, kymograph records) following a massive standard hemorrhage, on replacing the blood lost with an equal volume of one of the three solutions; (*b*) the permanence of the restoration of arterial pressure following *a* up to 2 hours; (*c*) the ability of the animals, after procedures *a* and *b*, to withstand a second hemorrhage. The pro-

cedures for withdrawing blood and injecting solutions were made as nearly standard as possible, particularly with respect to the rate of the hemorrhage or injection, and the time elapsing between the end of the hemorrhage and the beginning of the injection.

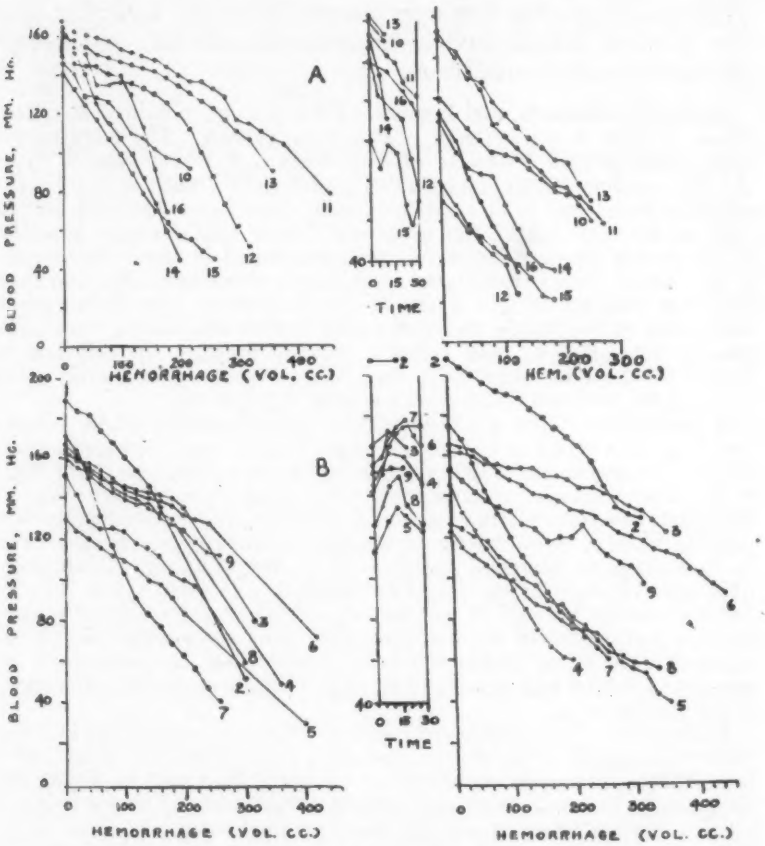

CHART 1.—Comparison of 5% glucose in 0.9% NaCl (*A*) with 8% to 10% gelatin in 0.9% NaCl (*B*). In both *A* and *B*, the curves on the left show the relationship in individual dogs (numbered on the curves) of arterial pressure to the volume of blood drawn in progressive hemorrhage (see text). The middle set of curves shows the change in arterial pressure with time following injection of either glucose-saline (*A*) or gelatin-saline (*B*). Time is given in minutes following completion of the injection. The curves on the right show the relationship of arterial pressure to the volume of blood drawn during second hemorrhage, begun in each case at the time indicated by termination of the preceding time record.

The data on gelatin are compared (Chart 1) with the data on a crystalloidal solution (glucose-saline). Blood was withdrawn in successive volumes of 20 cc., at intervals just long enough to permit arterial pressure to reach a relatively steady state after each withdrawal, until the pressure had been lowered critically. One minute after the termination of the hemorrhage, either gelatin or glucose-saline solution was injected in a volume equal to that of the blood which had been drawn. The rate of injection was

approximately 3 cc./kg. per minute. As is shown in the figure, the immediate restoration caused by the two solutions was not strikingly different. Following the injection, however, every animal receiving the crystalloidal solution showed a considerable fall in pressure (Chart 1*A*). In contrast, all the animals receiving gelatin (Chart 1*B*) showed a rise above the immediate postinjection level, usually reaching a peak within 10 to 15 minutes; and in no case was arterial pressure lower, at the end of 30 minutes, than immediately following the injection. Chart 1 also shows the difference in the ability of the two groups of animals to maintain arterial pressure during the second hemorrhage, performed in the same manner as the first and beginning up to 30 minutes after the injection. The animals receiving gelatin to replace the blood lost during the first hemorrhage, appeared to be as capable of maintaining arterial pressure during the second hemorrhage, as they had been originally (Chart 1*B*). On the other hand, those receiving glucose-saline invariably showed a greater fall in pressure for a given volume of hemorrhage, than originally (Chart 1*A*).

TABLE 1.—SUMMARY OF EXPERIMENTAL DATA.

			Initial hemorrhage.			B.P. after replacement.				Second hemorrhage.	
				B.P. at end.		Immediate.		30 min. later.			
Dog No.	Wt. (kilo).	Control B.P. (mm. Hg).	Vol. cc. A.	Mm. Hg.	% control.	Mm. Hg.	% control.	Mm. Hg.	% control.	Vol. cc. B.	Ratio, vol. B: vol. A.
					GLUCOSE-SALINE.						
10	8.0	146	280	80	54.8	160	109.6	..	..	140	0.5 : 1
11	12.6	162	440	76	46.9	152	93.8	120	74.0	220	0.5 : 1
12	9.1	164	320	50	30.5	148	90.2	78	47.6	80	0.25 : 1
13	10.3	160	360	86	53.8	162	101.2	..	..	200	0.55 : 1
14	5.9	166	200	44	26.5	150	90.3	..	..	140	0.7 : 1
15	7.4	140	260	44	31.4	100	71.4	70	50.0	120	0.46 : 1
16	5.2	150	180	68	45.3	144	96.0	112	74.7	80	0.44 : 1
Avg.	8.3	155.4	291	64	41.3	145	93.2	95	61.6	143	0.49 : 1
					GELATIN-SALINE.						
2	8.6	190	300	58	30.5	208	109.9	..	..	260	0.87 : 1
3	9.1	160	320	90	56.2	166	103.7	..	..	360	1.12 : 1
4	10.3	166	360	50	30.1	148	89.1	146	88.0	180	0.5 : 1
5	11.8	130	400	30	23.0	114	87.7	124	95.4	200	0.5 : 1
6	12.0	162	420	86	53.1	154	95.0	166	102.4	500	1.19 : 1
7	7.4	172	260	40	23.2	142	82.5	176	102.3	260	1.0 : 1
8	8.6	148	300	68	46.0	128	86.5	126	85.1	240	0.8 : 1
9	7.4	164	260	116	70.7	156	95.1	..	..	240	0.92 : 1
Avg.	9.4	161.5	327.5	67.2	41.6	152	93.7	147.3	94.6	280	0.86 : 1

Table 1 summarizes the pertinent data of Chart 1, as a basis for a quantitative comparison of the two solutions. As is shown in the table, in both groups the average volume of blood drawn during the initial hemorrhage amounted to approximately 40% of the animal's estimated blood volume (calculated as 8% of body weight). Arterial pressure at the end of this type of hemorrhage averaged 41.4% of the control. Although the immediate restoration of arterial pressure was nearly complete and equal with the two solutions, after a lapse of 30 minutes, pressure in the glucose-saline group had fallen to 61.6% of the control, while in the gelatin group it was still at 94.6% of the control. The last two columns in the table show the volume of blood which had to be drawn during the second hemorrhage in order to approximate the arterial pressure reached after the first hemorrhage, and the ratio of this volume to the volume of the initial hemorrhage. For the glucose-saline group, the ratio of the volume of the second hemorrhage, to that of the first (both resulting in lowering the blood pressure to approximately equal levels) was 0.49:1; for the gelatin group, the ratio

averaged 0.86:1. On the basis of these criteria, the relative ability of gelatin and glucose-saline solutions to replace blood as circulating fluid for a period of 30 minutes, may be arbitrarily expressed as the ratio 86:49.

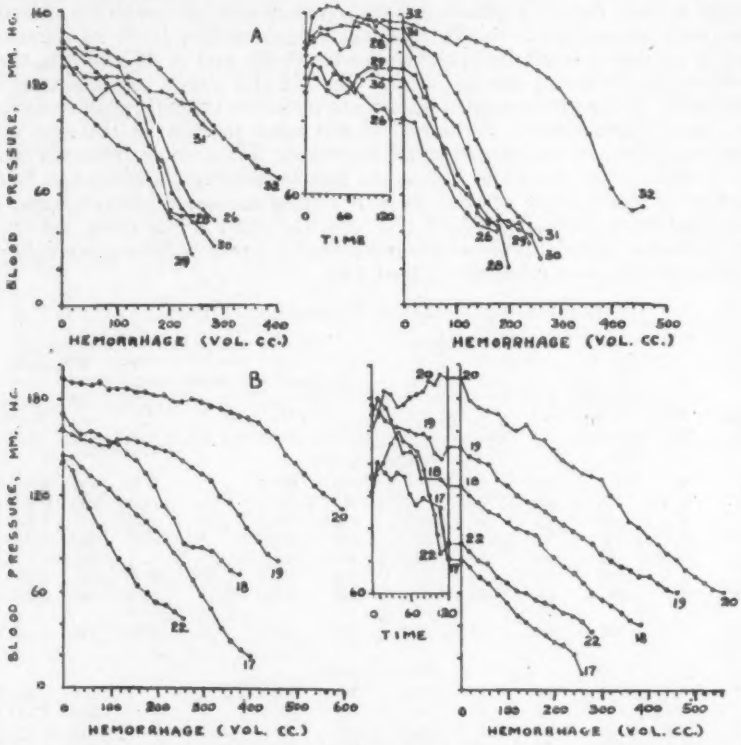

CHART 2.—Comparison of defibrinated blood (*A*) with 8% to 10% gelatin in 0.9% NaCl (*B*). Construction of figure exactly as in Chart 1.

A comparison of gelatin with defibrinated blood is shown in Chart 2. The experiments were carried out in the same manner as those described above, except that arterial pressure was followed for 2 hours after the initial hemorrhage and injection. As is shown in Chart 2*B* there was usually no fall in pressure below the immediate postinjection level for the first hour in the dogs receiving gelatin. There was usually, however, considerable lowering of pressure during the second hour (the average lowering during the entire 2-hour interval is 14% of the immediate postinjection pressure). The animals receiving defibrinated blood (Chart 2*A*) serve as a control, for all the experiments reported here, on the effects of the anesthesia and on the effect of the temporary reduction of blood volume during the first hemorrhage, with optimum replacement. As is shown in this Chart, these animals as a rule maintained a fairly constant arterial pressure throughout the period of observation following restoration of the blood volume lost during the initial hemorrhage. They also showed only a slight loss of ability to maintain pressure during the second hemorrhage. The dogs receiving gelatin started the second hemorrhage with a lower pressure than did those receiving blood, but as a rule showed a more gradual reduction in pressure as the hemorrhage progressed, a phenomenon deserving of further study.

Discussion. The ability of the cardiovascular system to maintain arterial pressure during severe hemorrhage is probably as rigorous a test as can be applied to the system. An interpretation of such a test in terms of the separate factors which govern arterial pressure, such as blood volume, blood viscosity, the work of the heart, tone of arterioles, and so on, is obviously impossible[8] without additional data. It appears, however, to offer certain advantages, in addition to its simplicity, in an investigation of this sort, where interest centers primarily about the ability of the circulation to keep itself going, and where the mechanism which enables it to do so is of secondary concern. On the basis of such a test, gelatin appears to be definitely superior as a blood substitute to glucose-saline, although, as might be expected, it is inferior to defibrinated blood. This conclusion is supported by the other data presented here, which show that gelatin solutions restore arterial pressure after it has been lowered by hemorrhage, for a considerably longer time than does glucose-saline. Again, in this respect, gelatin solutions appear to be inferior to defibrinated blood. That the elevation of arterial pressure produced by the gelatin is not due merely to its effect in increasing blood viscosity[2,6] is suggested by the fact that pressure continues to rise for 10 to 15 minutes after the injection, as it does after injecting defibrinated blood. Such a postinjection rise would be expected if the injection increased the colloidal osmotic pressure of blood, and so permitted blood volume to increase for a time after the injection was completed. Obviously, this interpretation cannot be given with assurance without data on blood volume.

A clinical study of the effect of intravenous injection of these gelatin solutions in human subjects is now in progress.[7] The results thus far obtained have been encouraging, since no severe reactions have followed transfusion with our solutions. It appears that gelatin from this particular source, prepared according to the directions given here, is without immediate toxicity for the human as well as for the dog. One of the early objections to gelatin for intravenous use, namely, that heating it to sterilizing temperatures would cause toxic decomposition,[1] does not seem to be applicable to the gelatin which we studied. In view of possible variation in gelatin even from the same source, test solutions are prepared from each new batch, autoclaved, cultured, and tested on the dog for toxicity.

The question of antigenicity for the human cannot be answered from our data on the dog, or the data of others.[9,10] Although gelatin is usually regarded as non-antigenic, the possibility of antigenic contaminants cannot be dismissed lightly when dealing with such an impure substance. A thorough investigation of this question is planned.

A final clinical evaluation of gelatin solution as a blood or plasma substitute will have to be postponed until the question of antigenicity for the human is settled. It cannot be predicted with

assurance whether gelatin will show any superiority over crystalloidal solutions in a vascular system damaged by shock, since our comparative data were obtained by study of a system which is normal except for the effects of anesthesia.

Since this study was begun, a number of publications have appeared on purified bovine albumin as a substitute plasma colloid.[5] Although the available data show that this material is non-toxic and capable of maintaining the circulation, data on its antigenicity for the human are lacking. Occasional subjects are reported as giving positive reactions to intradermal injection.[3] Since the determination of antigenicity for materials injected intravenously is largely on an empirical basis, data on this point will accumulate slowly. In view of the urgency of the present need for transfusion fluids it would be premature, therefore, to discontinue study of other blood substitutes.

Summary. Etherized dogs were subjected to massive hemorrhage under controlled conditions, and the volume of blood drawn was replaced immediately with defibrinated blood, with a heat-sterilized solution of bone gelatin 8 to 10% in 0.9% NaCl, or with 5% glucose in 0.9% NaCl.

All three of these solutions produced practically complete immediate recovery of arterial pressure. The restoration of pressure with defibrinated blood was still practically complete at the end of 2 hours. The restoration with gelatin was usually still complete at the end of the first hour, and approximately 86% complete at the end of the second hour. The restoration with glucose-saline was only 62% complete at the end of 30 minutes. The dogs restored with gelatin suffered no greater fall in pressure during second hemorrhage than did the dogs restored with defibrinated blood. The dogs restored with glucose-saline, however, were less able to withstand second hemorrhage than those of the other two groups.

No effects on arterial pressure or respiration suggesting the presence of toxic proteoses or amines in these autoclaved gelatin solutions were observed in dogs receiving up to 20 cc. kg. without previous hemorrhage (7 dogs) or in dogs receiving up to 90 cc. kg. after hemorrhage (38 dogs). Anaphylactoid reactions were not observed in animals (2 dogs) injected with 40 cc. kg. of gelatin solution 9 to 11 weeks after a sensitizing injection of 40 cc. kg. No pathologic changes were demonstrable on necropsy in any of the animals used in this study, including the two latter animals.

Conclusions. Gelatin solutions appear to occupy an intermediate position between blood and crystalloidal solutions in their ability to maintain the circulation after blood loss. The restoration of the circulation by gelatin lasts sufficiently long to cover many clinical emergencies. Since the samples of gelatin which have been tested can be made up in solution and autoclaved to sterility without the development of demonstrable toxicity for the dog, further study with a view to clinical trial is indicated.

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STUDIES ON THE HEMORRHAGIC AGENT, 3,3′-METHYLENEBIS (4-HYDROXYCOUMARIN).

II. The Method of Administration and Dosage.*

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In 1939 Prof. Karl Paul Link[2,3,5,9] and his associates isolated and crystallized the active principle in spoiled sweet clover that was responsible for the hemorrhagic disease of cattle. Shortly thereafter a series of brilliant investigations culminated in the synthesis of a compound that was identical in biologic characteristics to the isolated principle. This substance is 3,3′-methylenebis (4-hydroxycoumarin).†

In a previous report[1] it was demonstrated that the administration of this dicoumarin either orally, or intravenously in the form of the disodium salt, is succeeded by protracted prolongation of the prothrombin time and coagulation time in dogs and human beings. This effect follows an initial latent period of 24 hours or more succeeding the exhibition of the material. No untoward symptoms attended the administration of this substance in therapeutic amounts, but excessive quantities produced spontaneous hemorrhages and fatalities in dogs. Postmortem examination with gross and microscopic studies did not reveal significant pathologic change

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† Hereafter in this paper this specific substance frequently will be referred to as dicoumarin for the sake of simplicity, even though other dicoumarin derivatives are under investigation.

in the liver or kidneys; but it did show, in many animals, widespread dilatation of capillaries, arterioles, and venules. No lesions in the walls of the vessels were observed. At the time of the original communication the potential hazards of this dicoumarin and its possible advantages over heparin were discussed.

When the previous report was published, 3,3′-methylenebis (4-hydroxycoumarin) had been given to only 22 patients. The first 16 had received small doses, 2 mg. per kilo or less, and the results were either negligible or very moderate. In the remaining 6, the effects were striking. Since July, 1941, the substance has been given to 51 patients of varying ages, of both sexes, and under a wide variety of clinical conditions. Thus to date we have administered the material to 73 patients. This communication reports the results of administering this dicoumarin to human beings and suggests the proper dosage.

Methods. The prothrombin time was determined on undiluted plasma with Pohle and Stewart's modification[6] of Quick's method. On each day that tests were made 1 or more untreated patients were tested; these served as a control for check upon the technique and potency of the thromboplastin. Ordinarily the thromboplastin was of such potency that the normal prothrombin time for human beings was 9.5 to 10.5 seconds. The approximate percentages of prothrombin in human plasma as derived from the chart of Pohle and Stewart are as follows: a time of 12.5 seconds indicates a concentration of about 50% of normal; 19 seconds, 25% of normal; and 30 seconds, 12.5% of normal. A time longer than 45 seconds was generally less accurate because of the greater difficulty in determining the end point.

The coagulation time was measured at room temperature by the 2-tube method of Lee and White. Great care was taken to make sharp venipunctures, to have a free flow of blood, to avoid too great suction in the collection of samples, to avoid air bubbles, and to transfer the blood to the test tubes with a minimum of agitation. The tubes were scrupulously clean and the syringe clean and wet. By this method the normal coagulation time ranges from 6 to 12 minutes.

Materials. 3,3′-Methylenebis (4-hydroxycoumarin) was used exclusively in oral administration experiments; the disodium salt of this substance, which was in concentration of 10 mg. per cc. and at a pH of 10, or slightly higher, was the only material used intravenously. These materials were furnished us through the kindness of Professor Link and Dr. Stahmann.

Patients. The patients had a wide variety of diseases. The object of administering the dicoumarin was to establish a proper and safe dosage rather than to test the therapeutic efficacy of the substance. Six of the patients had thrombosis, but in the rest there was no such indication for the drug. Many of the patients, particularly those studied earlier, were in advanced stages of a malignant disease. Both sexes were represented, ranging in age from 10 to 73 years.

Complete blood counts, urine analyses, blood sugar and non-protein nitrogen determinations, and the Rumpel-Leede tourniquet test were done in all cases. In many, but not all, the hippuric acid liver function test, the cephalin-cholesterol flocculation test,[4] the icterus index, the bleeding time, and phenolsulphonphthalein renal function test were done before and after completion of observation. In a few, platelet counts were made. In no instance were there significant quantitative changes in the tests; neither

was there evidence that the hepatic or renal function was impaired as a result of the administration of the dicoumarin. In a few patients the control tests of hepatic function indicated the existence of liver damage. In these instances particular caution was exercised during and after the administration of the dicoumarin.

Results. *Intravenous Administration.* The disodium salt of 3,3′-methylenebis (4-hydroxycoumarin) has been given intravenously in varying doses to 27 patients. Of these, 24 received only 1 dose, 3 received repeated (2 to 5) doses. The single doses ranged from 0.5 mg. per kilo in 2 patients to 6 mg. per kilo in 1; the majority (15) received 4 mg. per kilo. The 3 patients who had repeated doses were given 4 mg. per kilo each time. The smallest doses

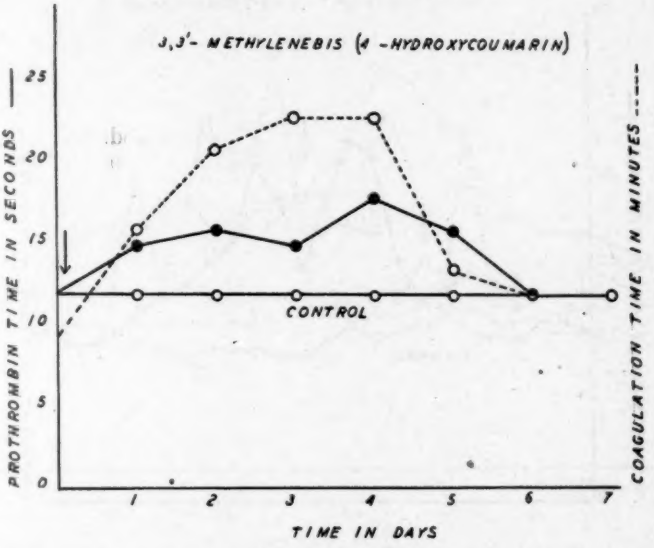

CHART 1.—Effect of an intravenous dose (4 mg. per kilo) of dicoumarin upon the prothrombin time and coagulation time of a 70-kg. white male. The control line indicates the prothrombin time in an untreated patient.

produced relatively little or no effect; the most effective single or repeated dose seemed to be about *4 mg. per kilo.* The patients did not all respond identically to a given dose. In all cases, without regard to size of dose, there was a latent period of about 24 hours before a demonstrable effect took place. After one dose there was a usual period of from 2 to 5 days before the maximal effect was noted, after which there was a gradual return, over a period of 3 to 5 days, of the prothrombin time and coagulation time to normal. The effects of a single intravenous dose are shown in Chart 1 and the effects of repeated intravenous administration of the dicoumarin are shown in Chart 2. This route of administration was studied to determine the latent period and to rule out the variable factor of

absorption. It appeared to have no significant advantage over the oral administration in those cases that are able to take medication by mouth.

Oral Administration. 3,3′-Methylenebis (4-hydroxycoumarin) has been given orally to 46 patients in single or repeated doses, varying from 0.75 mg. per kilo to 6 mg. per kilo. In early studies most of the patients received single and small doses. As we became more familiar with the effects of the drug, larger and repeated doses were given. For a time it was customary to give repeated large doses orally every 3 to 6 days, but in recent months it has been the rule to give an original large dose and subsequent daily small doses,

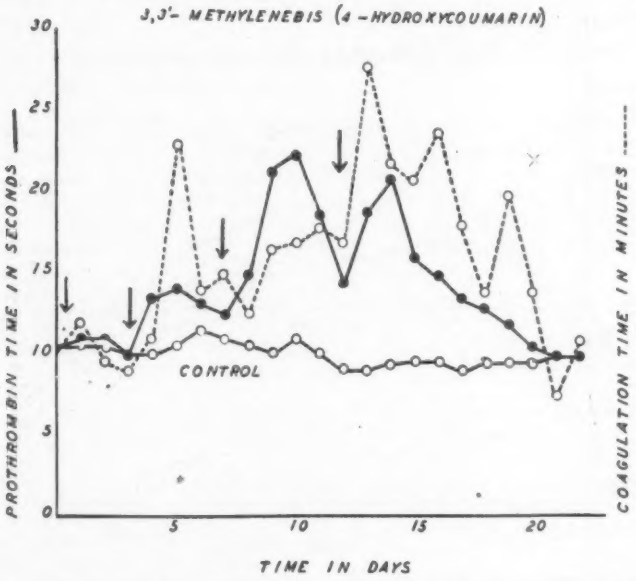

CHART 2.—Effect of 4 intravenous doses (4 mg. per kilo) of dicoumarin on the prothrombin time and coagulation time of a 65-kg. white male.

since this seemed to be the best method of maintaining a more uniform prolongation of prothrombin time and coagulation time. Typical responses to a large dose followed by daily small doses and to repeated large doses are shown in Charts 3 and 4.

The latent period, more prolonged, and the protracted effect upon the prothrombin time and coagulation time is demonstrated here as in the experiments where the drug was administered intravenously.

At present it is customary to give an initial dose of *5 mg. per kilo and to follow it with daily doses of 1.5 mg. per kilo.* This dose is nearly always effective. The response to this dose varied considerably. In some patients the prolongation in prothrombin time and coagulation time was greater than was desired. When this occurred,

the material was withheld for 1 or more days, until there was a trend toward normal. It is imperative when using this anticoagulant to make daily determinations of the prothrombin and the coagulation time.

It was found that an initial dose of 5 mg. per kilo followed by daily doses of 1 mg. per kilo produced a satisfactory response in 5 of 16 patients. With an initial dose of 5 mg. per kilo, followed by daily doses of 1.5 mg. per kilo, however, satisfactory response was noted in 11 of 14 patients; the results are shown in Table 1.

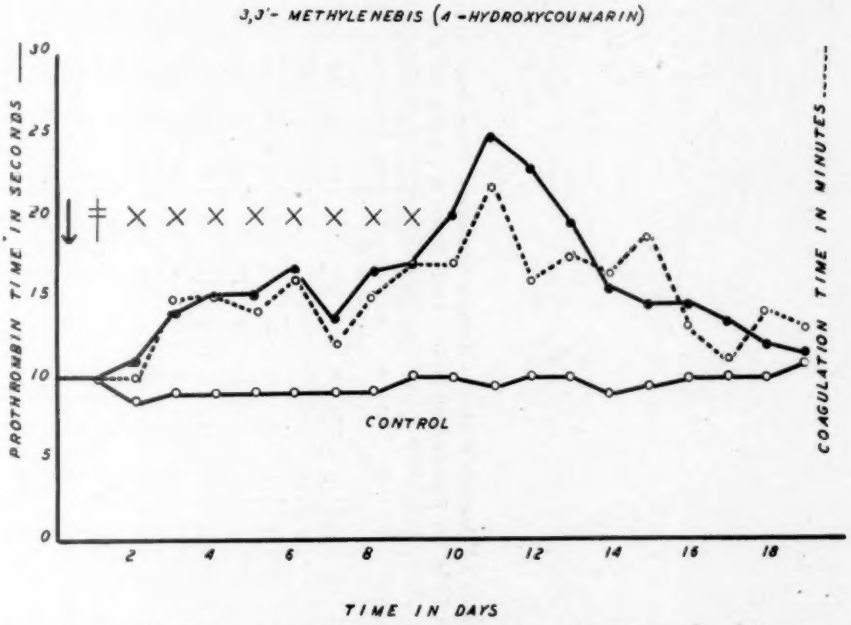

CHART 3.—Effect of repeated oral doses of dicoumarin on the prothrombin time and coagulation time of a 66-kg. white male. ↓ indicates a dose of 5 mg. per kilo. ‡ a dose of 1.5 mg. per kilo and × a dose of 1 mg. per kilo.

The prolongation in the prothrombin and coagulation time in the patients represented in the table is significant in all but 3 instances. In Cases 1, 2, 3, 4, and 8 the prolongation in coagulation and prothrombin time was greater than is theoretically necessary and actually reached hazardous levels. Although microscopic blood was noted in the urine or feces of 6 of these 14 patients, when coagulability of the blood was least, gross hemorrhage occurred in only 1 patient (a recently studied case). This was protracted and severe enough to cause real concern, and hence some details are warranted here.

CASE 1.—Mrs. H. V. B., a 44-year-old housewife who weighed 237 pounds (108 kilo), had chronic endocervicitis. Preliminary studies, including bleeding and coagulation time, the Rumpel-Leede test, blood non-protein

TABLE 1.—THE EFFECT OF ORAL ADMINISTRATION OF 3,3′-METHYLENEBIS (4-HYDROXYCOUMARIN) UPON THE COAGULATION AND PROTHROMBIN TIME.
Original Dose of 5 Mg. per Kilo and Subsequent Daily Doses of 1.5 Mg. per Kilo.

No.	Pts.	Diagnosis.	Age.	Sex.	Wt. (kg.).	Days 1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.
1	E. W.	Coronary occlusion	68	M	91	10 *	9.5 *	12 *	12 *	13.5 *	15 *	22.5 *	18 *	15 *	16 *	18	26	22.5 *	28	23.5	25	25	22.5	16	13	..	11.5
						9.5	*9.5*	*9.5*	*9.5*	*9.5*	*11.5*	*17.5*	*17.5*	*18.5*	*21*	*22*	*28*	*21*	*32*	*20*	*20*	*23*	*22*	*13*	*16*		*8*
2	G. B.	Carcinoma of lung	63	M	62	10 *	10 *	9.5 *	12.5 *	14.5 *	17 *	19 *	20	18	19 *	20.5 *	27.5	23	16	18 *	17 *	18 T	15	18	16	11	10.5
						11	*9*	*8.5*	*11.5*	*15*	*21*	*22.5*	*32*	*23.5*	*26*	*27*	*44*	*27*	*15*	*20*	*20*	*26*	*17*	*15*	*14*	*12.5*	*12.5*
3	H. V. B.	Obesity	44	F	108	10 *	10 *	*	12.5 *	12 *	14.5 *	15 *	19.5 *	19.5	35 T	18 T	18	26.5 T	28 T	17	19	16	22 T	17	12	10.5	
						11	*10*		*12*	*15*	*23*	*18*	*23*	*23*	*38*	*17.5*	*15*	*21*	*30*	*17*	*17*	*22*	*22*	*13*	*13*	*13*	
4	A. W.	Aur. fibrill. with emboli	36	M	86	11 *	14.5 *	12 *	16 *	22.5	20.5 *	23	30	21	25	27	30	37	44	26	20	13	11.5	10.5			
						9	*13*	*16*	*21.5*	*26*	*24*	*36*	*25*	*27*	*21.5*	*30*	*32*	*31*	*39*	*25*	*19*	*13*	*9.5*	*16*			
5	J. M.	Peptic ulcer	41	M	57	10 *	10 *	*	12 *	11 *	12 *	13 *	15 *	15.5 *	23 *	16.5 *	19.5	17.5	22.5	18	15		11.5				
						9.5	*9.5*		*11.5*	*12.5*	*11*	*13*	*13*	*15*	*10?*	*15*	*22*	*19*	*17*	*15*	*13*		*8.5*				
6	W. S.	Cavernous sinus thromb.	10	M	23	10 *	12 *	13.5 *	13.5 *	16 *	16	17	15.5	14	13 T_1	10	10	9.5									
						9	*10.5*	*15*	*15*	*15.5*	*24*	*23*	*29*	*26*	*18*	*12*	*11*	*12*									
7	H. H.	Diabetes	57	M	81	11.5	9 *	9 *	10.5 *	13 *	12.5 *	12 *	15 *	15 *	16	14.5	14.5		13.5	12	12	10					
8	H. B.	Gonorrheal arthritis	25	M	68	10 *	10 *	9.5 *	11 *	11.5 *	13 *	13 *	14.5 *	13.5 *	18 *	16 *	25	20	11.5	10							
						10	*8*	*8*	*13*	*18.5*	*16.5*	*18*	*19*	*16*	*25*	*31*	*31*	*30*	*15*	*13*							

		thromb.				9	10.5	15	15	15.5	24	23	29	26	T_1 18	12	11	12													
7	H. H.	Diabetes	57	M	81	11.5	9 *	9 *	10.5 *	13 *	12.5 *	12 *	15 *	15 *	16	14.5	14.5		13.5	12	12	10										
8	H. B.	Gonorrheal arthritis	25	M	68	10 *	10 *	9.5 *	11 *	11.5 *	13 *	13 *	14.5 *	13.5 *	18 *	16 *	25	20	11.5	10											
						10	*8*	*8*	*13*	*18.5*	*16.5*	*18*	*19*	*16*	*25*	*31*	*31*	*30*	*15*	*13*											
9	A. S.	Gastric ulcer	46	M	55	9 *	9 *	10.5 *	12 *	12 *	*	12 *	13.5 *	13	14.5	13	11.5		11.5												
						10	*9*	*9.5*	*12*	*10.5*		*9.5*	*17*	*9*	*10*	*11*	*14*		*9.5*												
10	J. B.	Bronchiectasis	59	M	50	9 *	10 *	12.5 *	14 *	14 *	16.5 *	13.5	15	14.5	13.5	12	13		12												
						8	*9*	*10*	*14*	*16*	*18*	*14*	*19.5*	*10*	*9*	*8*	*11.5*		*9*												
11	G. P.	Bronchial asthma	49	M	58	9 *	9.5 *	11 *	13.5 *	16 *	18 *	15.5 *	17.5 *	22	24	18	13	11.5													
						8	*10*	*10*	*15.5*	*18*	*14*	*15*	*15*	*15*	*24*	*16.5*	*18*	*13*													
12	W. B.	Carcinoma of prostate	65	M	74	10 *	10 *	10 *	11 *	15 *	*	13.5	14.5	14.5	12.5	10															
						8	*8*	*10.5*	*11*	*14*		*10.5*	*14*	*12*	*14*	*11*															
13	H. G.	Arteriosclerosis	53	F	46	10.5 *	10.5 *	11 *		13 *	15	15	12	12	11																
						8.5	*9*	*9.5*		*9*	*13*	*13*	*10*	*10*	*9*																
14	J. T.	Hypertrophic arthritis	60	M	68	10 *	10 *	9.5 *	10 *	10.5 *		10 *	11	10	9.5																
						8	*9.5*	*9*	*10*	*11*		*9*	*13*	*12*	*8.5*																

First row—prothrombin time in seconds. Second row (*italics*)—coagulation time in minutes.
* indicates days on which dose was given. T indicates transfusions of 500 cc. fresh blood. T_1 indicates transfusions of 250 cc. fresh blood.

nitrogen and glucose determination, the cephalin-cholesterol flocculation test, and hippuric acid liver function test, were all within normal limits. She was given 540 mg. (5 mg./kilo) of this dicoumarin on the day that dilatation, biopsy, and cauterization of the cervix and curettage of the uterus was performed under cyclopropane and nitrous oxide anesthesia. Thereafter the patient received daily doses of 162 mg. (1.5 mg./kilo). On the fifth day following operation, 7 days prior to the regular menstrual period, she began to have vaginal bleeding. Bleeding was not excessive until the eighth postoperative day, when the drug was discontinued. On this day the coagulation time was 23 minutes, the prothrombin time 19.5 seconds. Profuse to moderate bleeding persisted for 9 more days. Five transfusions of fresh whole blood, 500 cc. each, were given between the ninth and eighteenth postoperative days, spaced as shown in the table. Despite the transfusions the hemoglobin fell from a level of 15.9 gm. on the day of operation to 11.1 gm. the day following the last transfusion. No gross bleeding was demonstrated from any other than the site of the operation.

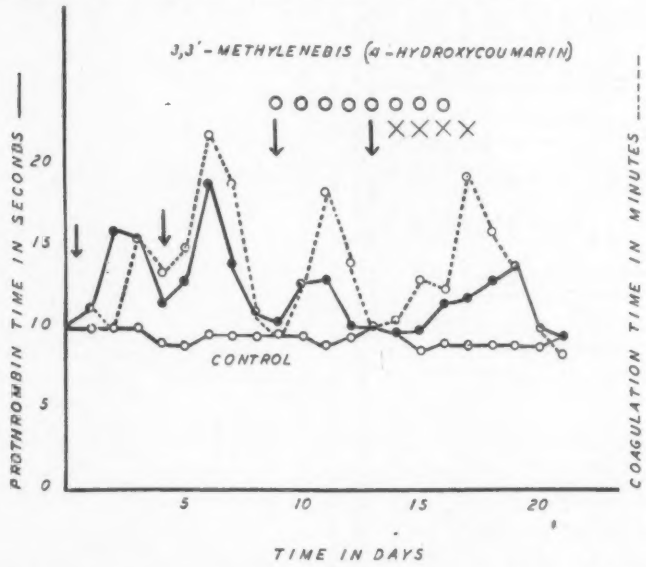

CHART 4.—Effect of repeated oral doses of dicoumarin on the prothrombin time and coagulation time of a 71-kg. white male. ↓ indicates a 5-mg. dose and × a 1-mg. dose. 0 indicates a 10-mg. oral dose of 2 methyl-1, 4-naphthoquinone. The negligible effect of the vitamin K administration is shown.

This patient gave us much concern during the period of bleeding. The first 4 transfusions were temporarily beneficial but not completely corrective. It is possible that larger quantities of blood might have been more effective. By the eighteenth postoperative day the patient had not received the dicoumarin for 9 days. It may be said that the administration of the substance to a patient that has had currettement of a mucous membrane surface is unusual and the risk of hemorrhage is great.

This case emphasizes one of the inherent limitations in the use of this dicoumarin, namely, the protracted decrease in coagulability of

the blood. The effect may be great and prolonged for days after the medication has been stopped, thus suggesting a cumulative effect of the drug. A similar effect had been previously observed in dogs.

Effect of Vitamin K. It has been shown that the simultaneous administration of vitamin K orally or intramuscularly to dogs in 1-mg. and 2-mg. doses did not inhibit the prothrombin-lengthening effect of the dicoumarin. Recent studies demonstrate that doses as large as 10 mg. of 2-methyl-1, 4-naphthoquinone to human beings do not prevent the lengthening of the prothrombin time and coagulation time. Chart 4 demonstrates the lack of gross effect of synthetic vitamin K upon the prothrombin and coagulation time.

Effect of Transfusions. Although the administration of vitamin K is not an antidote for the effects of the dicoumarin, it has been our experience that a transfusion of blood will shorten the prothrombin time and coagulation time. A quantity greater than 500 cc. may occasionally be necessary for satisfactory results. This effect is often transient, usually of about 24 hours' duration, and repetition of the transfusion may be necessary. This corrective effect confirms the finding of Schofield[8a,b] and Roderick[7] that the lives of cattle with serious hemorrhage can be saved by transfusions of serum or whole blood.

The effect of transfusions has been demonstrated 13 times in 8 patients. Fresh blood was found to be preferable, but bank blood, if not too old, appeared to be partially effective. The effect in the one case where fresh citrated blood was used is shown in Case 3 (Table 1), details of which are given above. This was the only case where transfusions were given to control bleeding. After 4 of the 5 transfusions the bleeding was less but not completely controlled. In other patients with less marked prolongation of prothrombin and coagulation time, transfusions were effective in bringing about a temporary return to normal levels.

Discussion. The use of 3,3′-methylenebis (4-hydroxycoumarin) to prolong coagulation of the blood in human beings appears feasible. Its administration, orally or intravenously, cautiously carried out, has not been attended by any symptoms of toxicity other than hemorrhage. Blood in microscopic quantities, as demonstrated by positive benzidine tests, appeared in the urine of 10 of the 73 patients at the height of the response. In 4 patients occult blood by the guaiac test was found in the stool. The case cited above, where curettement of the uterus was performed at the time the dicoumarin was being administered was the only one where gross bleeding occurred. The bleeding was restricted to the operative site.

The advantages of the dicoumarin as a possible substitute for heparin in the prevention of thromboses are quite obvious. The dicoumarin may be produced relatively cheaply, it may be given by mouth or intravenously, and a prolonged effect is obtainable. The

therapeutic index appears to be high. Doses as great as 25 mg. per kilo may be given intravenously to dogs without producing serious effect, whereas doses of 3 to 5 mg. per kilo will produce the desired prolongation of coagulation. The inevitable latent period after administration is a disadvantage in certain cases where immediate prolongation of the coagulation time is desired. There is, however, no theoretical objection to immediate treatment with heparin and subsequent substitution of the dicoumarin. The probable additional disadvantages are the apparent greater toxicity of this dicoumarin in excessive doses and the fact that once the coagulation is prolonged it cannot be shortened quickly by withholding the drug. We have given this drug in suitable doses orally each day for as long as 5 weeks without discernible toxic effect.

Whether or not 3,3′-methylenebis (4-hydroxycoumarin) or one of its derivatives will be efficacious, as heparin appears to be, in preventing thrombosis, is still to be determined. Our main purpose to date has been to establish a reasonably safe dosage. We have given it to only 6 patients with thromboses and to none for the distinct purpose of preventing thrombosis. Much study will be necessary to settle this major point of therapeutic efficacy.

This dicoumarin is potentially capable of inducing undesirable hemorrhage even in a dosage which is considered to be within the therapeutic range. It is our firm belief that its indiscriminate use would be extremely hazardous, and we urge that those who employ it administer the minimal effective dose and avoid its use where gross hepatic disease is known to exist. Because of considerable individual variation in response, it is imperative for the present that the prothrombin time and coagulation time be measured not less often than once a day. The desired degree of prolongation of coagulation is not known with certainty, but it appears that a coagulation time of approximately 15 to 20 minutes should be suitable and not too hazardous. Prolongation in the prothrombin time to between 12.5 and 19 seconds (approximately 50% to 25% of normal) is probably reasonably safe. At the 19-second level the percentage of prothrombin in the blood by the method we use is approximately 25%, and lower levels are not desirable.

At the present time it is our opinion that simultaneous determinations of the prothrombin time cannot be omitted. Although the lessening of coagulability of the blood is crucial, a check upon the cruder technical procedure of determining the coagulation time of whole blood is desirable. The determination of the prothrombin time is less subject to error in the hands of trained workers.

The administration of 3,3′-methylenebis (4-hydroxycoumarin) produced prolongation of the prothrombin time and coagulation time. Whether or not the coagulation time is prolonged because of the decrease in prothrombin is not established beyond question although there is, in most instances, a parallelism. The manner in which the dicoumarin acts to produce prolongation in the pro-

thrombin time after the latent period is not known. The theory that seems most attractive is that it acts as a physiologic inhibitor of prothrombin formation by the liver and that during the latent period the prothrombin of the blood is depleted. This possibility of liver inhibition is strengthened by the fact that vitamin K administration in adequate dosage is ineffective in preventing the increase in prothrombin time.

A second possibility is that the prothrombin produced in the presence of the hemorrhagic agent is altered in such a way that it is inactivated. The latent period might be due to some change that the dicoumarin must undergo in the body during the latent period before it is capable of functioning. Studies in progress by W. R. Sullivan, R. S. Overman, M. A. Stahman, and K. P. Link indicate that the hemorrhagic action takes place after the molecule of the compound has undergone certain changes in the body.

Conclusions. 1. The administration of 3,3′-methylenebis (4-hydroxycoumarin)—here referred to as dicoumarin—to human beings produced prolongation in the prothrombin time and coagulation time. The dosage and mode of administration have been discussed.

2. The minimal effective dose should be employed. The necessary dose for the desired decrease in coagulability of the blood varies with the individual case; but it appears that an initial oral dose of 5 mg. per kilo with subsequent daily oral doses of 1.5 mg. per kilo is effective in most patients. A single intravenous dose of 4 mg. per kilo was found to be suitable and effective. This dose may be repeated when necessary.

3. During the period of observation the prothrombin time and coagulation time should be determined not less often than once daily. If the increase of prothrombin time or coagulation time becomes too great, the dicoumarin should be withheld temporarily, and, if necessary, blood transfusions of 300 to 600 cc. should be given.

4. One patient who received dicoumarin following curettage of the uterus developed gross hemorrhage locally. No other gross toxic effects attended the use of the material in 73 patients.

5. The administration of vitamin K did not prohibit or correct the prothrombin deficiency produced by 3,3′-methylenebis (4-hydroxycoumarin).

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THE RENAL BLOOD FLOW, GLOMERULAR FILTRATION RATE AND DEGREE OF TUBULAR REABSORPTION OF GLUCOSE IN RENAL GLYCOSURIA.*

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Although various studies have indicated that true renal glycosuria is not associated with renal disease[1,5,9] or derangement in glomerular function,[16] no comprehensive and quantitative study has been made of the renal blood flow and the degree of renal tubular reabsorption of glucose at increasing plasma concentrations of glucose in this condition.

This communication presents simultaneous measurements of the glomerular filtration rate, the renal blood flow, the filtration fraction and the tubular reabsorption of glucose at different plasma concentrations of glucose in 5 patients with moderate renal glycosuria and in 7 controls.

Methods. The diodrast and inulin clearance methods were utilized for the estimation of the effective renal blood flow and the rate of glomerular filtration respectively. The same procedure for these two determinations was followed as previously described[7] except that the priming infusion in the present investigation consisted of (*a*) 50 cc. of 10% inulin solution, (*b*) 50 cc. of 50% glucose and (*c*) 1 cc. of 35% diodrast solution. The sustaining infusion consisted of (*a*) 100 cc. of 10% inulin solution, (*b*) 400 cc. of 50% glucose solution, (*c*) 5 cc. of 35% diodrast solution and (*d*) 250 cc. of normal saline. All clearances were adjusted to 1.73 sq. m. of surface area.

Blood samples were taken 30, 60, 90 and 120 minutes after the sustaining infusion had been started. Total urine collections were taken 45, 60, 75, 90, 105 and 120 minutes after the sustaining infusion had been started. For the first 30 minutes, the sustaining infusion was allowed to enter at a rate of 3 cc. per minute. This rate was increased 2 cc. every 30 minutes so that, at the end of the experiment, the patient was receiving 10 cc. of sustaining infusion per minute. At the end of 60 minutes, the patient was also given an additional 50 cc. of 50% glucose solution. In this manner, the three

* This study was aided by a grant from the Department of Medical Research of the Winthrop Chemical Company.

essential measurements were determined at constantly increasing blood glucose concentrations.

The blood and urine collections were analyzed for glucose, according to the method of Folin,[6] diodrast iodine, according to the method of White and Rolf[17] and inulin, according to the method of Alving and associates.[2]

The determination of tubular reabsorption of glucose was performed according to the principles given by Shannon and Fisher[15] and Goldring, Chasis, Ranges and Smith.[8] The glucose filtered through the glomeruli was calculated as the product of the inulin clearance X the plasma concentration of glucose. The tubular reabsorption of glucose was calculated as the difference between the amount of glucose filtered through the glomeruli (mg. per minute) and the amount of glucose found in the urine (mg. per minute).

The renal glucose reabsorption index (R.G.I.) was calculated as the ratio: $\frac{\text{glucose filtered through glomeruli (mg. per minute)}}{\text{glucose reabsorbed by tubules (mg. per minute)}}$. This index was used because it allowed a comparative evaluation of the degree of tubular reabsorption of glucose in any particular case, regardless of the rate of glomerular filtration. Diminished reabsorption, then, would be expressed by a high index, increased reabsorption, by a low index.

The 7 normal individuals studied had normal blood pressure and had no signs or symptoms of kidney disease. The urine of each was negative for detectable glucose by the Benedict test before and two hours after the ingestion of 100 gm. of glucose. The fasting plasma sugar of each was also within normal limits.

The pertinent data concerning the patients with renal glycosuria are given below. Each of the 5 patients had a glycosuria without hyperglycemia; the sugar in the urine was found to be glucose; and all urine specimens were found to contain detectable glucose. In 4 of the 5 cases, there was no progression in the glycosuria, despite the fact that they had been observed over several years. The fifth case was discovered 3 weeks prior to our examination. These cases then conform in general to the essential criteria postulated by Marble.[12]

CASE 1. E. N., male, aged 41, was known to have had renal glycosuria for at least 6 years prior to the present examination. He had no symptoms. The fasting plasma concentration of glucose was 86.2 mg. per 100 cc. and the fasting urine concentration of sugar was 118.3 mg. per 100 cc. The plasma concentration of glucose, 30, 60 and 120 minutes after the oral ingestion of 100 gm. of glucose was 134.2, 146.0 and 91.7 mg. per 100 cc. respectively. The sugar concentrations of the urine collections taken at the same time intervals were 202.0, 449.4 and 206.2 mg. per 100 cc. respectively. The chemical and microscopic examination of the urine was within normal limits.

CASE 2. L. L., male, aged 49, was known to have had renal glycosuria for at least 3 years prior to the present examination. He had no symptoms. The fasting plasma concentration of glucose was 81.6 mg. per 100 cc. and the fasting urine concentration of sugar was 158.8 mg. per 100 cc. The plasma concentration of glucose 30, 60 and 120 minutes after the oral ingestion of 100 gm. of glucose was 77.0, 123.5 and 133.0 mg. per 100 cc. respectively. The sugar concentrations of the urine collections taken at the same time intervals were 138.0, 300.8 and 330.6 mg. per 100 cc. respectively. The chemical and microscopic examination of the urine was otherwise negative. The blood pressure was within normal limits.

CASE 3. N. P., male, aged 30, was known to have had renal glycosuria for at least 5 years prior to the present examination. He had no symptoms. The fasting plasma concentration of glucose was 83.7 mg. per 100 cc. and the fasting urine concentration of sugar was 238 mg. per 100 cc. The plasma concentration of glucose 30, 60 and 120 minutes after the oral ingestion of 100 gm. of glucose was 69.7, 106.4 and 97.1 mg. per 100 cc. respectively. The sugar concentrations of the urine collections taken at the same time intervals were 336, 320 and 340 mg. per 100 cc. The chemical and microscopic examination of the urine was otherwise negative. The blood pressure was within normal limits.

CASE 4. J. C., male, aged 40, was known to have had renal glycosuria for at least 3 weeks prior to the present examination. He was first seen in the Department of Medicine, University of California Medical School, and was referred to us for further study. He had no symptoms. The fasting plasma concentration of glucose was 74.6 mg. per 100 cc. and the fasting urine concentration of sugar was 155.0 mg. per 100 cc. The plasma concentration of glucose 30, 60 and 120 minutes after the oral ingestion of 100 gm. of glucose was 155.6, 158.8 and 63.9 mg. per 100 cc. respectively. The sugar concentrations of the urine collections taken at the same time intervals were 347.8, 384.6 and 357.2 mg. per 100 cc. respectively. The chemical and microscopic examination of urine was otherwise negative. The blood pressure was within normal limits.

CASE 5. F. Y., male, aged 35, was known to have had renal glycosuria for at least 5 years prior to the present examination. He had no symptoms. The fasting plasma concentration of glucose was 90.9 mg. per 100 cc. and the fasting urine concentration of sugar was 46.5 mg. per 100 cc. The plasma concentration of glucose 30, 60 and 120 minutes after the oral ingestion of 100 gm. of glucose was 141.8, 141.4 and 142.6 mg. per 100 cc. respectively. The last plasma sugar remained elevated because an 18% glucose solution was given intravenously 110 minutes after the beginning of the glucose tolerance test. The sugar concentrations of the urine collections taken at the same time intervals were 183.4, 540.4 and 695 mg. per 100 cc. respectively. The blood pressure was within normal limits.

TABLE 1.—CLEARANCE DETERMINATIONS IN NORMAL AND RENAL GLYCOSURIC INDIVIDUALS.

Case No.	Name.	Age.	Effective renal bloodflow (cc. per min.).	Renal inulin clearance (cc. per min.).	Filtration fraction %.
			A. *Normal.*		
1	H. R.	43	1400	108	12.8
2	E. B.	16	1370	109	12.4
3	K. D.	32	..	145	
4	O. F.	23	1640	234	20.3
5	F. K.	32	..	116	
6	R. R.	23	1035	110	19.0
7	S. S.	50	865	112	21.7
Average			1262	133	17.2
			B. *Renal Glycosuria.*		
1	E. N.	41	1500	159	19.6
2	L. L.	49	1470	118	13.9
3	N. P.	30	1010	127	20.4
4	J. C.	40	1435	127	14.8
5	F. Y.	35	930	103	20.9
Average			1269	127	17.9

Results. A. *The Renal Blood Flow and Glomerular Filtration in the Normal and Glycosuric Individual.* No abnormal change in the

effective renal blood flow, the rate of glomerular filtration or the filtration fraction was found in the 5 renal glycosuric patients studied. The average effective renal blood flow was 1262 cc. per minute in the 7 control patients (see Table 1) and 1269 cc. per minute in the glycosuric patients. The average inulin clearance was 133 cc. per minute in the control and 127 cc. per minute in the glycosuric group. The close similarity of these values with those previously reported by us[7b] indicates also that the production of a hyperglycemia and its accompanying profuse diuresis does not change the renal blood flow or glomerular filtration.

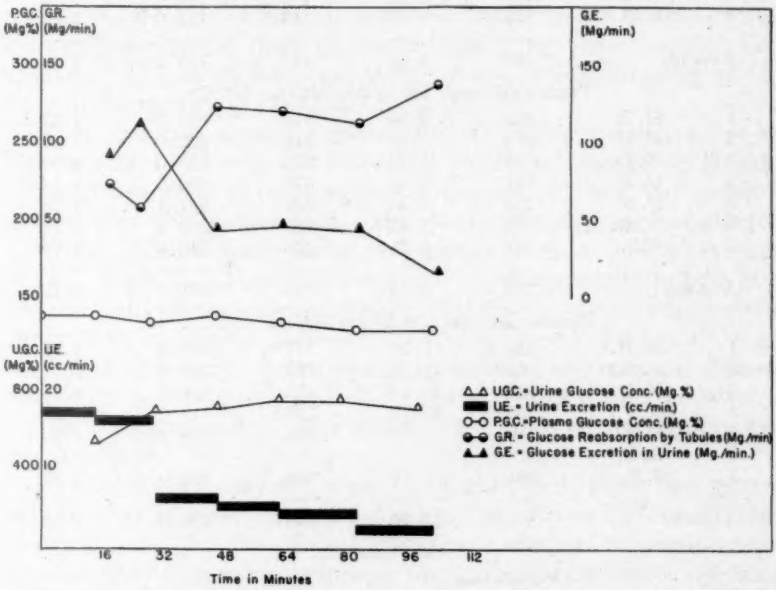

CHART 1.—Relation of tubular reabsorption of glucose to excretion of urine at constant plasma concentrations of glucose. The dependence of urinary glucose concentration upon the plasma concentration of glucose also is shown (Case F. Y.).

B. *The Tubular Reabsorption of Glucose in the Normal and Glycosuric Individual.* In both the normal and the glycosuric individual, it was found that the urinary concentration of glucose at high plasma glucose levels (100 to 400 mg. per 100 cc.) was relatively independent of the rate of urine excretion but was directly proportional to the concentration of glucose in the plasma. This independence of the urine concentration of glucose and the rate of urine excretion is illustrated in Chart 1. Here, the plasma glucose is maintained at a constant level and the rate of urine excretion decreases. Nevertheless, there is little change in the urinary concentration of glucose. The degree of tubular reabsorption, therefore, at a constant plasma concentration of glucose (Chart 1), increases with

TABLE 2.—THE GLOMERULAR CLEARANCE AND TUBULAR REABSORPTION OF GLUCOSE IN NORMAL AND IN RENAL GLYCOSURIC INDIVIDUALS AT INCREASING BLOOD GLUCOSE LEVELS.

Normal.

Plasma Glucose, 100 to 200 Mg. per 100 Cc.

Case No.	Name.	Plasma glucose concentration (mg. per 100 cc.).	Urine flow (cc. per min.).	Glomerular clearance of glucose (mg. per min.).	Tubular reabsorption of glucose (mg. per min.).	Renal glucose reabsorption index.
1	H. R.	116	6.60	123	120.0	1.03
2	E. B.	140	4.20	159	155.0	1.03
3	K. D.					
4	O. F.	115	6.66	273	268.0	1.02
5	F. K.					
6	R. R.	162	2.05	160	159.0	1.02
7	S. S.	129	1.50	145	141.0	1.03
Average		132	4.20	172	169.0	1.03

Plasma Glucose, 200 to 300 Mg. per 100 Cc.

1	H. R.	298	3.58	316	300.0	1.05
2	E. B.	275	5.60	312	292.0	1.07
3	K. D.	263	3.45	373	358.0	1.04
4	O. F.	241	8.20	575	504.0	1.14
5	F. K.	254	7.50	264	207.1	1.28
6	R. R.	292	3.60	289	261.0	1.11
7	S. S.	247	4.70	278	246.0	1.13
Average		267	5.23	344	309.0	1.12

Plasma Glucose, 300 to 400 Mg. per 100 Cc.

1	H. R.	356	7.36	377	350.0	1.08
2	E. B.	385	12.35	438	385.0	1.14
3	K. D.	338	10.50	476	436.0	1.10
4	O. F.	305	16.10	727	618.0	1.18
5	F. K.	380	11.75	395	298.0	1.32
6	R. R.					
7	S. S.	341	4.70	384	349.0	1.10
Average		351	10.46	466	406.0	1.15

Renal Glycosuria.

Plasma Glucose, 100 to 200 Mg. per 100 Cc.

1	E. N.	140	3.84	186	168.3	1.11
2	L. L.	128	10.80	175	139.0	1.26
3	N. P.	102	2.30	140	131.0	1.07
4	J. C.	111	4.04	141	126.6	1.12
5	F. Y.	133	3.15	160	137.3	1.17
Average		123	4.83	160	140.4	1.15

Plasma Glucose, 200 to 300 Mg. per 100 Cc.

1	E. N.	270	5.00	431	399.8	1.08
2	L. L.					
3	N. P.	284	4.68	453	419.0	1.08
4	J. C.					
5	F. Y.					
Average		272	4.84	442	409.4	1.08

Plasma Glucose, 300 to 400 Mg. per 100 Cc.

1	E. N.	400	10.30	508	475.0	1.07
2	L. L.	310	14.60	425	419.0	1.02
3	N. P.	339	12.10	540	462.0	1.17
4	J. C.	321	2.10	407	394.0	1.04
5	F. Y.					
Average		347	9.77	470	437.0	1.08

decreasing urine flow. In any study then, of the renal tubular reabsorption of glucose in several groups of individuals, a comparison of the results may not be valid unless the plasma concentrations of glucose and the rates of urine excretion of both groups are approximately equal.

As Table 2 indicates, the kidney of the glycosuric individual at a moderate plasma level of glucose (100 to 200 mg. per 100 cc.) is less efficient than that of the normal individual in reabsorbing glucose contained in the glomerular filtrate. Whereas, in both types of individuals, the average plasma concentration of glucose, the glomerular clearance of glucose and rate of urine excretion were approximately equal, the average rate of tubular reabsorption of glucose was distinctly less in the renal glycosuric (140.4 mg. per minute). The average R.G.I., therefore, was higher in the glycosuric group (1.15) than in the control group (1.03).

When the two groups were studied at higher plasma levels of glucose (200 to 300 mg. per 100 cc.) it was found (see Table 2) that, although the tubular reabsorption of glucose (309 mg. per minute) increased in the normal group, the glomerular clearance of glucose (344 mg. per minute) increased relatively more. The average R.G.I. (1.12) therefore was increased. Unfortunately, only 2 glycosuric individuals were studied at this particular plasma glucose range, but, unlike the normal individuals, these 2 did not show an increased divergency between the glomerular clearance of glucose (442 mg. per minute) and the tubular reabsorption of glucose (409.4 mg. per minute). The average R.G.I. (1.08) accordingly was not increased.

Finally, the tubular reabsorption of glucose in these two groups was studied at a very high plasma level of glucose (300 to 400 mg. per 100 cc.). In the control group, the glomerular clearance of glucose (466 mg. per minute) was found again to have increased relatively more than the tubular reabsorption of glucose (406 mg. per minute). The average R.G.I. (1.15), accordingly, was increased. In contrast to these findings, there was no increasing divergency between the glomerular clearance of glucose (470 mg. per minute) and the tubular reabsorption of glucose (437 mg. per minute) in the glycosuric group. On the contrary, in the glycosuric individuals there was less inequality between these two renal functions at this plasma glucose range than at the lowest range studied. This last fact resulted in a lower average R.G.I. (1.08) for the glycosuric individuals at the maximum plasma glucose range studied. These results indicated that the efficiency of tubular reabsorption of glucose increased with rising plasma concentrations of glucose in the glycosuric individual and decreased in the control subjects.

Discussion. The studies herein reported indicate clearly that the effective renal blood flow, the glomerular filtration and the filtration fraction are within normal limits in the individual with moderate

renal glycosuria. Furthermore, the present observations indicate that, whereas tubular reabsorption of glucose in the glycosuric patient is less than that found in the non-glycosuric individual at moderate plasma concentrations of glucose (100 to 200 mg. per 100 cc.), this comparative diminution in reabsorption in the glycosuric subject disappears at higher plasma concentrations of glucose. As a matter of fact, it would appear as if the renal glycosuric individual absorbs glucose contained in the tubular fluid more efficiently than does the non-glycosuric individual at high plasma concentrations of glucose. This last observation makes it difficult to assume that a serious organic or physiologic derangement is present, either in the kidney or elsewhere, in the patient with moderate renal glycosuria; for one would not expect a fundamentally deranged organ to perform abnormally when not under stress and normally when under considerable stress.

Several investigators,[11,14] however, have attempted to incriminate the adrenal or parathyroid gland in this disorder. Their evidence, is not conclusive. Furthermore, other studies[3,4] have denied the relationship of any particular endocrine gland with the etiology of renal glycosuria.

Indeed, it is perhaps questionable whether the individual with moderate renal glycosuria should be considered abnormal in the pathologic sense, for there is uniform agreement[5,9,10] that a considerable portion of supposedly normal people will have glycosuria without hyperglycemia during the administration of a glucose tolerance test. Thus, the mild glycosuric individual may be the statistical victim of too close adherence to an average renal threshold value composed of widely scattered individual values. Certainly our results are compatible with this latter view.

Conclusions. 1. The effective renal blood flow (diodrast clearance) and the rate of glomerular filtration and the degree of renal tubular reabsorption of glucose were studied in 7 normal and 5 renal glycosuric individuals.

2. The effective renal blood flow and glomerular filtration in the renal glycosuric individual were found to be normal.

3. The lessened tubular reabsorption of glucose in the renal glycosuric individual does not appear to be due to an organic kidney defect, for at plasma glucose levels above 200 mg. per 100 cc., the efficiency of tubular reabsorption of glucose in these cases equals or exceeds that found in non-glycosuric individuals.

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IMMUNITY IN DIABETES.

IV. Measurements of Phagocytic Activity in Diabetes Mellitus.

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This study is part of an investigation of the well-known susceptibility of diabetic patients to infection. It is evident from clinical observation that this susceptibility varies with changes in the condition of the patient. In a previous paper[1c] it was suggested that, in such a study, all of the offensive and defensive properties, both of the infecting organism and of the tissues and fluids of the host, should be examined were this possible. It seems probable that at least some of these properties would differ in the diabetic as compared with the non-diabetic and also with the state of adjustment of the patient. In former papers of this series[4b] it has been shown that some of the constituent substances in the blood of diabetic patients and experimental animals show no significant alterations which would connect them with this deficiency in resistance. On the other hand, there does appear to be a significant correlation between some of these factors, such as the amount of glycogen in the tissues and of globulin in the blood, and the ability of the body to resist infection or at least to delay its effects. As regards the globulin, these observations would seem to be not altogether unexpected, as much previous work has shown that there exists a close connection between globulin and various phases of immunity.

The present study deals with the ability of the leukocytes of the host to phagocytize such bacteria as may be present in the body. The phagocytes are known to be affected by a number of conditions, some of which, it seems, might be altered in the diabetic patient depending on the state of adjustment. It has been shown that a decrease in the phagocytic ability of these cells occurs with lowered

temperature,[2] increased hydrogen-ion concentration and in the presence of certain substances, including iodine and lactic acid. Increase of cytoplasmic viscosity also has been reported as decreasing phagocytic action. On the other hand, addition *in vitro* of histamine, calcium ions and certain fat-soluble substances including iodoform, chloral hydrate, ethyl alcohol and low concentrations of chloroform, appear to increase phagocytosis. Turnya found a lowered phagocytosis in thyroidectomized rabbits. This was increased by feeding thyroid extract.[2]

Methods. In this study the phagocytic power of the leukocytes has been measured by a method devised by Boerner and Mudd.[1] This method consists in adding to 1 cc. of freshly drawn blood to which a small amount of heparin has been added, 0.1 cc. of a suspension of bacteria in physiologic saline, prepared so that the suspension always contains approximately the same number of bacteria. The dilution in these determinations was such that in each 0.1 cc. of suspension there were 200 million bacteria. As the fortuitous collision of cells and bacteria is an important factor in phagocytosis, a variation in the number of bacteria used will alter the number engulfed by the cells. The blood, with added bacteria, is agitated at 38° C. in the type of water bath devised by Boerner and Mudd.[1] At intervals of 3, 6, 9 and 12 minutes, a drop of blood is removed and smears are made on glass slides according to standard technique. After rapid drying, these smears are stained by Giemsa's stain and the number of bacteria in 100 leukocytes is counted. The "phagocytic score," which is the term used by Mudd and his associates to denote the phagocytic ability of the cells, as demonstrated by this method, expresses the number of bacteria taken up by 100 cells as a percentage of a theoretical maximum of 30 bacteria per cell. In these determinations, smears were made after 6 minutes and 12 minutes agitation. The results given in this paper were from slides made after 12 minutes. The *Staph. aureus* used in this investigation was obtained from the blood of a fatal case of bacteremia and has been maintained for the past 6 years by semi-weekly transplants on plain agar. Only smooth colonies are taken for transplant so that at the present time very few rough colonies appear in the culture. This same strain of *Staph. aureus* has been used throughout all of the experiments reported in this series of papers.

The sugar of the blood was determined by the modification of Folin's micro method, the final reading being made with an Evelyn photoelectric colorimeter. Bloor's method was used for determination of cholesterol and the Pregl-Kjeldahl method for total protein and for albumin after fractionation by a 22.2% solution of sodium sulphate at 37.5° C. Globulin was taken as the difference between the total protein and the albumin. The diabetic patients on whom these studies were made were taken from the Metabolic Clinic of this hospital and are typical of such patients in a fair state of metabolic adjustment. The normal controls were doctors, students and others connected with the clinic.

In order to examine the consistency of the method in our hands, duplicate determinations were done on 20 patients. The duplicates were carried out entirely separately, including the final counts, which were made by two of us.

The difference between these duplicates, taken at the same time, in measuring the phagocytic score of 20 diabetic patients ranged from 5 to 0 (average 2.5). The change between two measurements of phagocytic score, each an average of duplicates, on diabetic patients at intervals of from 1 to 3 months ranged, in 34 patients,

from +22 to —16 with an average change, regardless of sign, of 5.23. The phagocytic score of all 54 diabetic patients ranged from 13 to 53 (average 28); S. D. 1.12.

In Table 1 are shown the distribution of phagocytic scores in diabetic patients and normal controls. No significant difference can be recognized.

TABLE 1.—DISTRIBUTION OF PHAGOCYTIC SCORES IN NORMAL CONTROLS AND DIABETIC PATIENTS.

Phagocytic scores.	Normal controls (17).	Diabetic patients (78).
Above 40	29%	23%
20 to 40	53%	55%
Below 20	18%	22%

Number of observations is shown in parentheses.

At the same time that blood was taken for determination of the phagocytic score, blood was also removed for determination of the sugar and of the cholesterol, total protein and albumin of the serum. As has been stated, the serum globulin was measured as the difference between the total protein and the albumin. The results of these examinations are shown in Table 2.

TABLE 2.—CHEMICAL ANALYSES OF BLOOD AND PHAGOCYTIC SCORES IN PATIENTS WITH DIABETES.

	Patients not taking insulin.	Phagocytic score.	Patients taking insulin.	Phagocytic score.
Blood sugar	*Up to 139 mg. (28)*	26	Up to 139 mg. (32)	27
	140 mg. and above (20)	27	140 to 250 mg. (35)	28
			250 mg. and above (14)	27
Serum cholesterol	*Up to 255 mg. (8)*	27	Up to 255 mg. (26)	25
	256 to 349 mg. (22)	28	256 to 350 mg. (44)	29
	350 mg. and above (7)	28	350 mg. and above (12)	25
Serum protein	6.20% to 8.49% (26)	29	6.2% to 8.5% (54)	27
	8.50% and above (14)	25	8.5% and above (25)	28
Serum albumin	*Up to 4.2% (12)*	28	*Up to 3.8% (10)*	24
	4.3% to 5.7% (36)	26	3.9% to 4.2% (28)	28
			4.3% to 5.7% (36)	29
Serum globulin	1.3% to 3.3% (13)	31	1.3% to 3.3% (24)	25
	3.4% and above (24)	29	3.4% and above (58)	29

Number of observations in each group is shown in parentheses.

It appears from these figures that the variations in the chemistry of the blood commonly found in diabetes show no correlation with the phagocytic power of the blood. Phagocytic score varies little when the components measured in the chemical tests are exhibiting considerable variation. It will also be noted that the percentages of patients showing high, medium and low scores is similar to those found in the normal controls. On the whole, it would seem that diabetes in the absence of any marked complications does not alter the phagocytic power of the leukocytes as tested by this method.

Since it appears that reasonably well-balanced diabetic patients do not commonly differ from normal controls, in this test of the ability of the phagocytes to engulf bacteria, it seemed desirable to test the influence of various factors upon the diabetic patient's

phagocytic scores. For this purpose two common complications, acidosis and undernutrition, were selected and also the response of the diabetic to the stimulus of antityphoid vaccination. Six patients with acidosis were studied in this way. The results are shown in Table 3. Accompanying the leukocytosis, which is a common finding in this condition, there is a very definite decrease in the phagocytic score. The highest figure among the acidosis patients was only slightly higher than the lowest in those diabetics without acidosis. The average of the six examinations is 9 ± 1.4 as compared with 28 ± 2.0 in those patients shown in Table 2. The sugars of the blood varied as would be expected from 220 to 512 with four of them over 400. The total protein, albumin, and globulin, of the serum varied considerably, probably following the marked dehydration and other alterations of the blood and tissues in these patients. The serum cholesterol was not found to be as high as might have been expected, perhaps due to the short time during which the acidosis had developed.

TABLE 3.—PHAGOCYTIC SCORE OF DIABETIC PATIENTS WITH ACIDOSIS.

Patient.	Date.	Blood sugar, mg. per 100 cc.	CO_2 content, vols. %.	Serum cholesterol, mg. per 100 cc.	Serum protein, %.	Serum albumin, %.	Globulin, %.	Phagocytic score.	Age, yrs.
J. B.	12/ 9/38	488	16	287	9.94	4.50	5.44	8	37
D. Mc.	1/23/39	380	18	q.n.s.	6.90	5.39	1.51	10	19
R. M.	1/ 6/39	220	28	416	11.30	4.00	7.30	6	17
R. W.	1/16/39	512	30	219	7.87	3.98	3.89	8	16
M. L.	1/12/39	500	39	214	7.36	2.82	4.54	14	35
R. D.	3/18/39	486	19	316	8.32	4.09	4.53	8	29

Average phagocytic score, 9 ± 1.4.

In Table 4 are shown the phagocytic scores and the results of the blood chemistry determinations in 6 diabetic patients who came into the hospital after inadequate treatment. They were all in a marked state of undernutrition with the usual signs of an uncontrolled diabetes. While these patients did not show quite as low a phagocytic power as those in acidosis, nevertheless it was significantly lower than was found in those diabetic patients who were in a fair state of control. It will be noticed that the CO_2 content of the serum, while close to the lower limit of normal, is definitely above the figures found in the patients with acidosis. The phagocytic scores, while slightly above those present in acidosis, are still significantly lower than those found in diabetic patients without complications.

In the course of an investigation of the ability of diabetic patients and normal controls to form agglutinins after inoculation with *B. typhosus* vaccine, the phagocytic score was determined, using the *Staph. aureus* suspension, and the agglutinins in the serum were determined by Dreyer's macroscopic method using a formalized suspension of *B. typhosus*. The vaccine was given according to the standard method. Blood for determination of the phagocytic power against *Staph. aureus* and of agglutins against *B. typhosus* was taken before the first injection of the vaccine and 2 weeks after the third dose. Twelve diabetic patients and 8 normal controls were used. The patients varied in their state of adjustment. Five of them were in good condition, with hyperglycemia occurring only rarely, while the other 7 were less well balanced, yet in a fair state of adjustment, so that while hyperglycemia was not infrequent, there were no symptoms referable to the diabetes. The normal controls were members of a class of nurses entering the hospital at that time.

TABLE 4.—PHAGOCYTIC SCORE OF PATIENTS WITH UNCONTROLLED DIABETES.

Patient.	Date.	Blood sugar, mg. per 100 cc.	CO_2 content, vols. %.	Serum cholesterol, mg. per 100 cc.	Serum protein, %.	Serum albumin, %.	Globulin, %.	Phagocytic score.	Age, yrs.
W. H.	12/ 8/38	476	51	q.n.s.	10.50	3.90	6.60	10	24
M. B.	1/17/39	346	51	250	7.12	3.17	3.95	19	40
C. R.	2/ 2/39	488	52	312	7.65	4.73	2.92	11	18
R. K.	1/17/39	256	60	240	8.27	4.00	4.27	9	
G. W.	2/15/39	298	57	219	7.43	3.90	3.53	16	32
H. G.	3/28/39	384	53	354	8.62	4.09	4.53	12	26

Average phagocytic score, 13 ± 1.6.

Phagocytic scores against *Staph. aureus* and agglutinative titer against *B. typhosus* of these patients are shown in Table 5. It will be noticed that there is a significantly higher average in the phagocytic score in the normal controls after the vaccine as compared with the determinations made before the vaccine was given. On the other hand, no such difference is found in the patients before and after the vaccine; in fact, the average for these examinations are identical.

Inspection of Table 5 shows that after vaccination the controls exceed the diabetic patients both in phagocytic score and in agglutinative titer.

It has been generally believed that phagocytosis is influenced both by non-specific and by specific factors. These experiments show

that a non-specific increase in the activity of the phagocytes may occur following the injection of a bacterial antigen in the normal subject but that this increase failed to occur in the diabetics.

TABLE 5.—PHAGOCYTIC SCORE AND AGGLUTINATIVE TITER IN DIABETIC PATIENTS AND NORMAL CONTROLS BEFORE AND AFTER B. TYPHOSUS VACCINE.

	Before vaccine.		After vaccine.	
	Phagocytic score.	Agglutinative titer, dilution.	Phagocytic score.	Agglutinative titer, dilution.
Diabetic patients (12)	22	0	22	1 : 63
Normal controls (8)	21 ± 0.95	0	31 ± 1.50	1 : 540

Number of observations shown in parentheses.

During the progress of this work an investigation was being carried on with experimental animals. Depancreatized cats and normal controls were studied with respect to their ability to prevent the spread of bacteria to other parts of the body from a focus of infection in the skin. In addition to determinations of sugar of the blood and total protein, albumin and cholesterol of the serum, the phagocytic score against *Staph. aureus* was also determined. The results of these examinations confirm the observations reported above on diabetic patients. No alteration was found in the phagocytic score of depancreatized cats without complications as compared with that of normal control animals. On the other hand, those animals with a marked alteration in nutrition accompanying hyperglycemia showed a phagocytic score significantly lower than the control group. The animals with a large amount of acetone in the urine and a low CO_2 content of the serum also had a very low phagocytic score. No test of influence of typhoid vaccine on phagocytic score against *Staph. aureus* was made in these experimental animals but in an earlier study[4c] we found no difference in agglutination titer in typhoid vaccinated animals after depancreatization as compared with controls.

Discussion. It would appear from the above observations that the phagocytic power of the leukocytes is not affected by several alterations in blood chemistry that are commonly found in the diabetic patient who is in a fair state of control. This power may vary considerably but not more widely than is found in a group of normal controls. On the other hand, two complications of diabetes, namely, acidosis and the marked alteration in nutrition which often accompanies the extreme diabetic state, are associated with a significantly decreased ability on the part of the leukocytes to phagocytose.

Among the factors which are known to lessen phagocytosis are increased hydrogen-ion concentration of the body fluids. Increased viscosity of the fluids such as may be exhausted with dehydration, and the presence of organic acids diminish the activity of the phagocytes. Lactic acid especially is known to have an unfavorable influence on phagocytosis. These factors are all present to a greater

or less degree in the uncontrolled diabetic and may influence phagocytosis.

Furthermore, the stimulation of the phagocytic score against *Staph. aureus* by injection with typhoid vaccine occurs in the normal subject but not, in these experiments, in the diabetic patient. Taken with the inability of the diabetic organism to form agglutinins following *B. typhosus* vaccine, it would suggest that this restriction of response to stimulation may be an important factor in the failure of the diabetic organism to resist infection as well as controls.

Neufeld and Rimpau[3a,b] suggested that the thermolabile opsonin of Wright is, like complement, general in its action and that the thermostabile bacteriotropin, which they demonstrated in the serum after inoculation with pneumococci, is an antibody and specific in its action.

Support for Neufeld's theory is furnished by observations in this and former papers of this series. It has been shown[4a] that complement in the serum of diabetic patients does not differ significantly in amount from that of normal controls; similarly the phagocytic score before vaccine does not differ in diabetic patients and normal controls. On the other hand, it has also been shown[4a] that diabetics fail to form antibody in as high a titer after *B. typhosus* vaccine as do normal controls; similarly the diabetic patients are unable, after vaccine, to increase their phagocytic power as do normal controls. Before inoculation with vaccine we would be comparing opsonic activity in Neufeld's sense in the diabetic and control; after the use of vaccine the difference noted between diabetic and control would be referred to a difference in Neufeld's bacteriotropin.

Summary. 1. The phagocytic power of the leukocytes of diabetic patients and depancreatized cats and of normal controls has been determined (Boerner and Mudd[1]).

2. Phagocytosis is found not to differ from normal in diabetic patients or in depancreatized cats in which the chemistry of the blood is within the limits commonly found in this condition.

3. Diabetic patients and depancreatized cats with acidosis or those with uncontrolled diabetes show a significantly decreased phagocytic power.

4. An increase of phagocytic activity of blood leukocytes which occurs in normal controls after typhoid vaccine, did not occur in our diabetic patients.

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STUDIES ON GALACTOSE TOLERANCE WITH ESPECIAL REFERENCE TO THYROID DISEASE.

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To clinicians faced with the problem of the diagnosis of hyperthyroidism, any new diagnostic test is most welcome, especially in distinguishing low-grade hyperthyroidism from anxiety states associated with hyperventilation or cardiac insufficiency. Such a procedure was recently proposed by Althausen *et al.*[1a,3,4] in the form of an oral galactose tolerance test. Their studies suggested that in hyperthyroidism the occurrence of glycosuria, impaired dextrose tolerance and postprandial hyperglycemia were due to increased rate of absorption of sugar from the intestinal tract. In accordance with Verzar's views,[25] this increased absorption is due to accelerated phosphorylation in the intestinal mucosa. Evidence was presented to show that other factors such as carbohydrate depletion, increased rate of bloodflow, intestinal hyperperistalsis, elevated basal metabolism and increased permeability of the mucosa did not play a part in the increased rate of intestinal absorption.[2]

Galactose was used in this test because its rate of absorption from the intestinal tract was found to be similar to that of glucose. It had the added advantage of being easily isolated from other blood-reducing substances. In addition, only the liver can utilize galactose[8,9,11,17] and it is not influenced by insulin.[19] Furthermore, there is no renal threshold for galactose.[14] The results[1,3,4] indicated that the peak of the blood galactose in patients with hyperthyroidism after the oral administration of 40 gm. of galactose was three times that of normal subjects. The higher values were found at the 30 or 60 minutes' blood specimens and ranged between 10 to 30 mg. per 100 cc. for normal individuals. Values between 30 to 40 mg. per 100 cc. were considered in the doubtful range, while those over 40 mg. per 100 cc. were classified as definitely abnormal. In hypothyroid patients, the maximum rise in blood galactose did not exceed 10 mg. per 100 cc.

Althausen and his coworkers found that in patients with severe hyperthyroidism, the basal metabolic rate, however, was a better

indicator of the severity of thyrotoxicosis, although the galactose tolerance curves were also very high. Impaired galactose tolerance was also present in Paget's disease and in patients with jaundice due to parenchymatous liver involvement. Maclagan and Rundle[16] likewise found postabsorptive curves which were elevated in hyperthyroid patients but they suggested that these curves were due to impaired liver function.

The present investigation was undertaken to restudy and to supplement the previous findings of Althausen and his coworkers. Moreover, it appeared important to determine the effect of age and of clinical conditions other than hyperthyroidism on galactose tolerance.

Material and Method. An oral galactose tolerance test as described below was carried out on each of 85 patients. The following groups were segregated:

1. *Age Group.* Forty-seven patients; 24 were over the age of 50 and 23 under 50 years in whom no evidence of thyroid disease, impaired liver function or Bright's disease was disclosed.
2. *Hyperthyroidism.* Twenty patients; 16 with diffuse toxic goiter and 4 with toxic nodular goiter.
3. *Impaired Liver Function.* Seven patients; 5 with toxic hepatitis due to sulfonamide or gold therapy, 1 with fungus infection of the lung and possibly of the liver and 1 with chronic passive congestion of the liver.
4. *Bright's Disease.* Six patients; 5 with chronic diffuse glomerulonephritis and 1 with arteriosclerotic nephritis.
5. *Upper Respiratory Infections.* Nine patients with pharyngitis, laryngitis or sinusitis.
6. *Diabetes Mellitus.* Seven patients.
7. *Miscellaneous.* Sixteen patients; 3 with thromboangiitis obliterans, 4 with carcinoma or Hodgkin's disease, 4 with hypothyroidism, 1 with nontoxic nodular goiter and 4 with neurocirculatory asthenia.

An appraisal of hepatic function was also made in each patient by the following tests: urinary excretion of galactose,[5,7,22,23] bromsulphalein retention,[21] and serum cholesterol partition.

The method employed to determine galactose tolerance was similar to that outlined by Althausen *et al.*[4] with slight modifications. Following a 12 to 14 hour fast, venous blood specimens were drawn before and at intervals of 30, 60 and 120 minutes* after the oral administration of 40 gm. of galactose dissolved in 400 cc. of water. Blood glucose was removed by fermentation with Fleischmann's yeast according to the method of Somogyi.[24] The yeast was washed six or seven times.[4,18] Seven cubic centimeters of a 20% yeast suspension and 2 cc. of a tungstic acid solution (Folin-Wu[10]) was mixed with 1 cc. of oxalated blood. The mixture was filtered and 2 cc. portions were used for the sugar determinations.† Because the reducing power of galactose is less than that of glucose, the figures obtained were increased by 24% in order to give the true value for galactose.[4]

Results. In order to conserve space the individual galactose tolerance curves are not detailed. Chart 1 shows the mean galactose tolerance curves of 24 patients over the age of 50 and 23 patients under the age of 50. Patients with hyperthyroidism, hypothyroid-

* The original technique called for 5, 15, 30, 60 and 120 minute specimens of blood.

† With the technical assistance of Anna Mei-Lan Lee, B.A.

ism, impaired liver function or Bright's disease were eliminated from this group. It will be observed that the factor of age *per se* appears to exert little influence on galactose tolerance. It should be stated, however, that the range of the highest blood galactose (2 to 92 mg. per 100 cc.) obtained in this series of "control" subjects is wider than that reported by Althausen and his coworkers (5 to 45 mg. per 100 cc. Furthermore, 16, or 34% of the 47 patients comprising this group, showed impaired tolerance to galactose according to the standards originally described by Althausen *et al.*

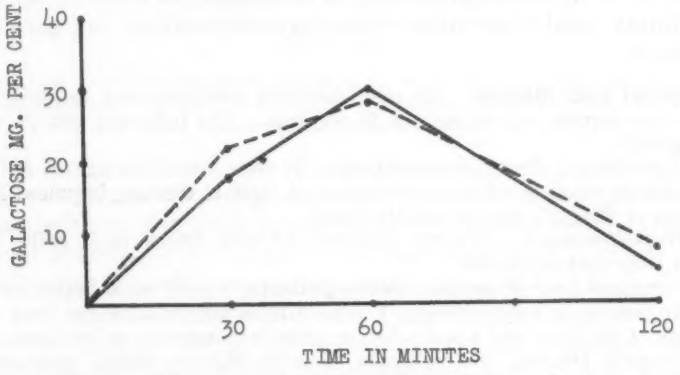

CHART 1.—The mean galactose tolerance curves of 24 patients over 50 years of age (broken line) and 23 patients under 50 years (solid line) without hyperthyroidism, hypothyroidism, impaired liver function or Bright's disease.

Chart 2 shows the average galactose tolerance curves of 20 patients with hyperthyroidism, 7 patients with impaired liver function, 6 patients with Bright's disease, 9 with upper respiratory infections and 7 with diabetes mellitus. The impaired galactose tolerance in patients with hyperthyroidism is clearly demonstrated. The range of the peak of the individual curves (17 to 136 mg. per 100 cc.) compares well with that of Althausen *et al.* (25 to 152 mg. per 100 cc.). Only 1 patient in this group showed a normal tolerance to galactose, which may be accounted for by the fact that there was marked evidence of regression of thyroid activity as indicated by sections of thyroid tissue obtained during subtotal thyroidectomy. It was further observed that there was no correlation between the basal metabolic rate and the degree of impairment of galactose tolerance. The mean galactose tolerance curve for the 7 patients with impaired liver function was moderately high. Analysis of individual curves of these patients indicated that even slight impairment of liver function without the presence of jaundice may be reflected in an abnormal curve. It is interesting to note that 4 of these patients had recently received sulfonamide therapy for lobar pneumonia and that the galactose tolerance test was carried out approximately 1 week after the cessation of the drug. Chart 2

further shows that the average galactose tolerance curves for 6 patients with Bright's disease and for 9 patients with upper respiratory infections were also moderately high. The composite curve for 7 patients with diabetes mellitus was not abnormal.

A heterogeneous group of 16 patients was also studied but the results were not included in Chart 2. Two of the 4 patients with hypothyroidism, peculiarly enough, showed impaired tolerance to galactose which was ascribed to the fact that thyroid extract was taken for its therapeutic effect. This was not unlike the abnormally high galactose tolerance curves found in normal rats fed thyroid

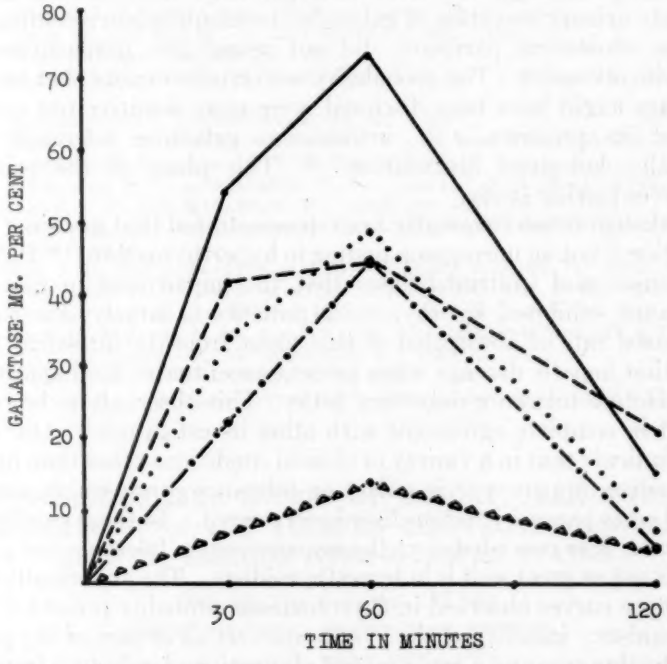

CHART 2.—The mean galactose tolerance curves of 20 patients with hyperthyroidism (solid line), 7 patients with impaired liver function (broken line), 6 patients with Bright's disease (dotted line), 9 patients with upper respiratory infections (dot and dash line) and 7 patients with diabetes mellitus (triangle line).

extract.[2] Four patients with neurocirculatory asthenia gave a normal response to the oral administration of galactose. This finding is important because the galactose tolerance test appears to have its greatest value in the differentiation of this syndrome from true hyperthyroidism, frequently a confusing diagnostic problem. Three patients with carcinoma and 1 with Hodgkin's disease gave abnormally high galactose tolerance curves.

Comments. The present study confirms the findings of Althausen and his coworkers[1a,b,3,4] insofar as abnormally high galactose toler-

ance curves are noted in patients with hyperthyroidism. The pitfalls of this test, however, may lie in such clinical conditions as are associated with liver damage even to a slight degree and in the absence of hyperthyroidism. The presence of jaundice is known to interfere with the interpretation of this test[4], but it is now shown that patients with Bright's disease, upper respiratory infections and possibly malignant disease may also give moderately high galactose curves. Moreover, patients who have recently received sulfonamide therapy may show impaired tolerance to galactose. It is conceivable that hepatic damage may account for the abnormal curves noted in these disorders, although the liver function tests used in this study, namely urinary excretion of galactose, bromsulphalein retention and serum cholesterol partition, did not reveal any parenchymatous liver involvement. The probability nevertheless exists that hepatic damage might have been disclosed, were more sensitive test used to detect its presence, *e. g.*, intravenous galactose tolerance[6] and cephalin-cholesterol flocculation.[13,20] This phase of the problem deserves further study.

Although it has frequently been demonstrated that impaired liver function is not an uncommon finding in hyperthyroidism,[12,15] Bassett, Althausen and Coltrin[6] believe that the impairment in galactose tolerance exhibited by thyrotoxic patients is largely due to the increased rate of absorption of this sugar from the intestinal tract and that hepatic damage when present accentuates the impairment in galactose tolerance only very little. This observation, however, is not in complete agreement with other investigators.[16] Our findings indicate that in a variety of clinical conditions other than hyperthyroidism impairment in galactose tolerance exists which may be ascribed to parenchymatous liver involvement. In these conditions, however, it is conceded that the impairment in tolerance for galactose is not as great as it is in hyperthyroidism. The abnormally high galactose curves observed in thyrotoxicosis probably present a dual mechanism: inability of the liver to convert all or part of the galactose to glycogen and a rapid rate of absorption of galactose from the intestinal tracts.

Conclusions. 1. The factor of age, *per se*, appears to exert little or no influence on the galactose tolerance curve.

2. Patients with hyperthyroidism, Bright's disease, upper respiratory infections, malignant disease and those who have recently received sulfonamide therapy frequently demonstrate impairment in galactose tolerance following the oral administration of this sugar. The impairment in galactose tolerance, however, is most marked in patients with thyrotoxicosis, which may be ascribed to a dual mechanism: (*a*) increased rate of absorption of this sugar from the intestinal tract and (*b*) hepatic damage.

3. Patients with diabetes mellitus are shown to have a normal tolerance for ingested galactose.

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THE ESTROGEN-LIKE ACTION OF DESOXYCORTICOSTERONE ACETATE UPON THE ALTERED ELECTROCARDIOGRAM SEEN IN VARIOUS HYPO-OVARIAN STATES.

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Among a variety of commonly observed symptoms and signs in woman with ovarian dysfunction and in those undergoing a "natural" or surgical menopause, alterations of the electrocardiogram may appear, which involve chiefly the final deflection.[11]

Relatively small doses of estrogen bring about a normalization of the electrocardiogram within a short time. Since a hypersecretion of corticotropic hormone in patients with ovarian hypofunction was assumed to be one of the causes of the vascular disturbances, and

since a close chemical relationship exists between the estrogens and the corticosterols, we have studied the effect of administration of desoxycorticosterone acetate* in a series of patients with disturbed ovarian function and altered electrocardiograms.

Case Reports. Case 1. H. A., a woman of 27 was admitted to the hospital for palpitation, nervousness, great fatigue, and anxiety. A panhysterectomy had been performed 8 years previously. Two years before admission, the patient received a series of injections of an estrogenic hormone. She has been treated for "neurocirculatory asthenia."

Physical examination of the heart revealed a normal form and size, but with evidence of a marked hypermotility; the sounds were pure, and the blood pressure on admission was 120/90. There was no evidence of organic heart disease. The patient had not received digitalis or any other medicine prior to admission.

The first electrocardiogram (Fig. 1*A*), taken on entry to the hospital, showed a sinus rate of 85, a normal conduction time, and a slight slurring of the QRS-complexes. The T-wave in Lead I was low. In Lead II there was a depressed S-T segment followed by an almost invisible T-wave. In Lead III and in the chest lead (CR_2), the S-T segment was depressed, and the T-wave inverted. Figure 1*B* was taken 13 days later after the administration of 3 injections of 10,000 IU estrogen. At that time, all of the patient's symptoms had disappeared, and she was very euphoric. In the electrocardiogram the pulse rate was as before; however, the T-waves were higher in Lead I, normally positive in Lead II, and much less inverted in Lead III and the chest lead.

No medication was given for 8 days, when the patient complained again of her former symptoms and of excessive fatigue. The electrocardiogram taken at that time is reproduced in Figure 1*C*. The heart rate had increased to 106, the S-T segment in Lead II was again depressed, and the T-wave in that lead was lower. The inversion of the T-wave in Lead III and in the chest lead is again more pronounced. At this time 10 mg. of desoxycorticosterone acetate were given daily for 3 days. The patient again experienced a marked improvement, although she did not feel as relaxed and free from fear and fatigue as after the first series of injections. The electrocardiogram taken 5 days after that in Figure 1*C* (Fig. 1*D*) showed a marked change. There was a bradycardia of 40. The S-T segments were normal in each lead, and the T-waves were positive. One week later the patient complained of some hot flushes, pressure over the precordium, and excitability; these symptoms gradually increased. Figure 1*E*, taken 12 days after Figure 1*D*, again suggested a marked deterioration with changes which are almost like those of Figure 1*C*.

Case 2. C. C., a woman of 26, was admitted for malnutrition and 'hypo-ovarianism." Six years previously the patient had had an operation for oöphoritis and salpingitis. Since that time her menstrual flow has lasted only 1 to 2 days and has been scanty. She had suffered from pain over the precordium, dyspnea, and palpitation. On examination, there were no signs of hyperthyroidism. The heart exhibited a normal size and form, but tachycardia and hypermotility were both present. The heart sounds were pure, and the blood pressure was 108/76. No organic cardiovascular disease existed. The patient did not receive digitalis before admission.

The first electrocardiogram, taken on admission (Fig. 2*A*), showed a sinus tachycardia of 130 and a marked depression of the S-T segment in

* Desoxycorticosterone acetate for these studies was kindly supplied through the courtesy of Dr. Max Gilbert of the Schering Corporation and by Roche-Organon, Inc.

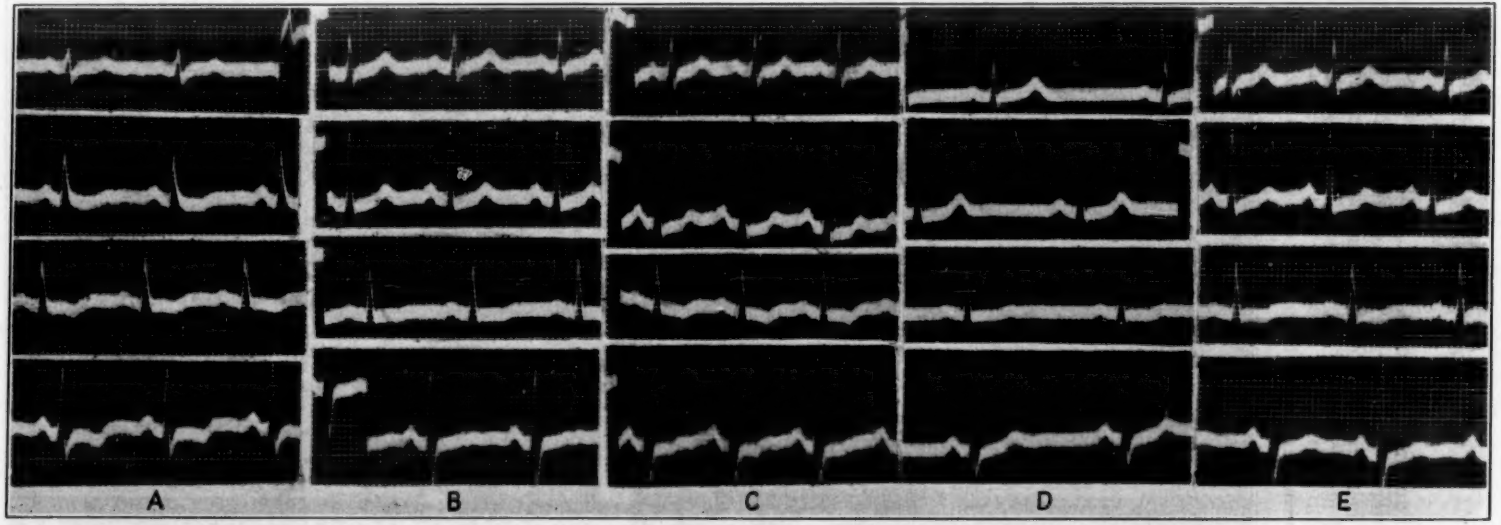

FIG. 1.—Case 1. *A* shows electrocardiogram before, and B following treatmentwith estrogenic hormone. *C* was taken 8 days later, and *D* after administration of desoxycorticosterone acetate. *E* was taken 12 days later.

each limb lead and in the chest lead (CR_4). After 5 injections of 10 mg. of desoxycorticosterone acetate, the electrocardiogram became normal (Fig. 2*B*), and the heart rate fell to 104. The patient experienced great relief from many of her symptoms, but still believed herself to be "under high tension."

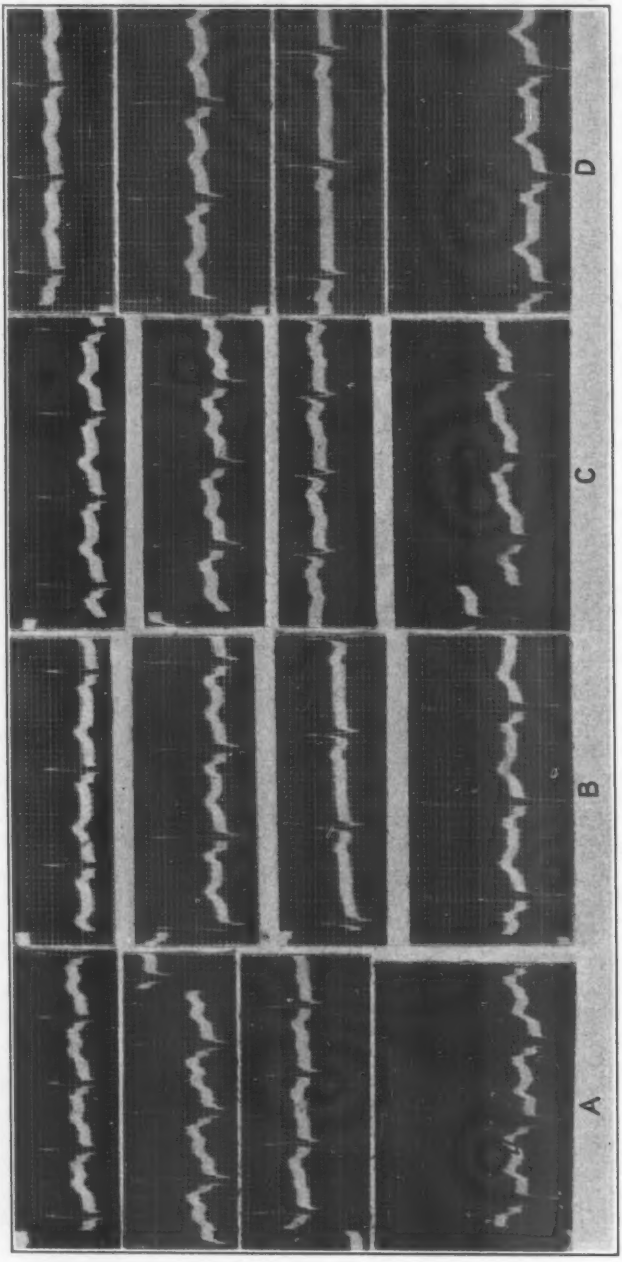

FIG. 2.—Case 2. *A* was obtained before, and *B* after treatment with desoxycorticosterone acetate. *C* was taken 2 months later. *D* was obtained after treatment with estrogenic hormone.

The next electrocardiogram (Fig. 2*C*) was taken 2 months after Figure 2*B*; no medications had been used in the interim. It showed a return of a tachycardia of 120 and a depression of the S-T segments in Leads II, III, and the chest lead. The T-wave in the chest lead had disappeared. Figure 2*D* was obtained 1 week after Figure 2*C*; in the meantime the patient had received 2 injections of 10,000 IU each of estrogenic hormone. She felt much better and showed a perfectly normal electrocardiogram.

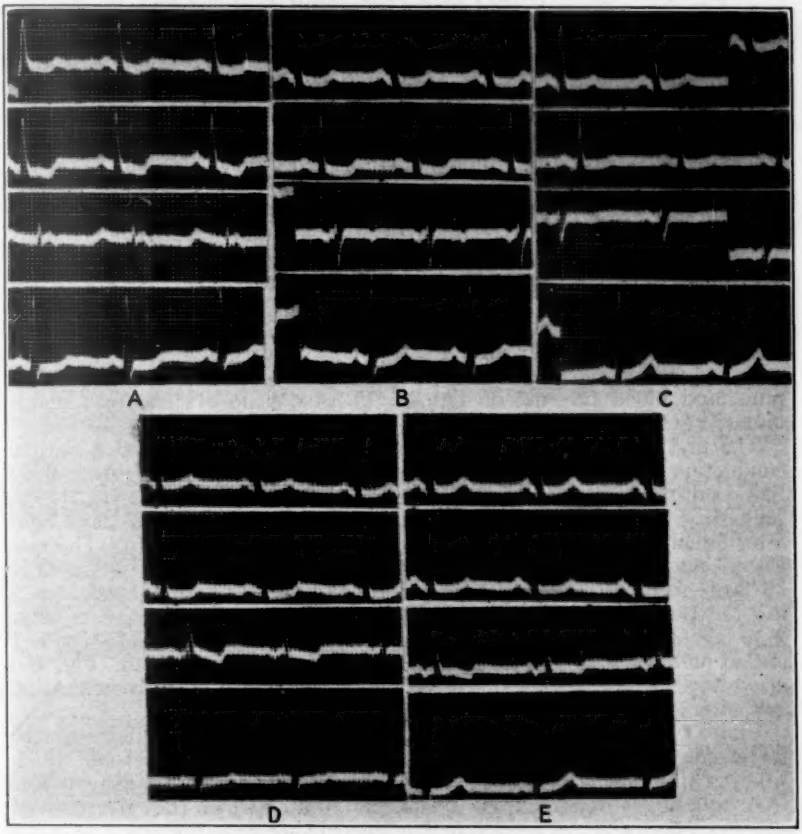

FIG. 3.—Case 3. *A* was taken before, and *B* after injections of desoxycorticosterone acetate. *C* was made after treatment with estrogen; *D* was obtained 8 months later, and *E* was obtained after treatment with desoxycorticosterone acetate.

CASE 3. K. C., a woman of 47, was readmitted to the hospital 4 weeks after an operation for prolapsus uteri. She complained of precordial pain, dyspnea, and flushes. Physical examination did not reveal any signs of an organic heart lesion. The slightly obese patient had a heart which was normal in size and form. The second aortic sound was slightly accentuated, the heart sounds were pure, and the blood pressure was 100/60, and the blood Wassermann test was negative. The patient did not receive digitalis before admission, and there were no abnormal findings besides uterine fibroids.

The first electrocardiogram, taken on admission (Fig. 3*A*), showed a regular sinus rhythm with a marked depression of the S-T segment, especially in Lead II and in the chest lead. The T-waves were abnormally low. Figure 3*B* was taken 1 week later after injection of 10 mg. of desoxycorticosterone acetate daily for 4 days. There was a marked improvement, the depression of the S-T segments had diminished, and the T-waves became positive. A series of 7 injections of 2000 RU estrogen caused a complete normalization of the electrocardiogram (Fig. 3*C*, obtained 10 days later.)

The patient was reëxamined 8 months later, at which time hot flushes, palpitation, and so forth, were again present. The electrocardiogram (Fig. 3*D*) showed a normal Lead I, but an abnormal S-T segment and an abnormal T-wave in Lead II and the chest lead. A series of 6 injections of 10 mg. of desoxycorticosterone acetate administered twice weekly caused a complete disappearance of these changes with normalization of the electrocardiogram and marked improvement in subjective symptoms.

CASE 4. E. F., a woman of 47, seen through the courtesy of Dr. George Lutton, was admitted to the hospital because of weakness, loss of weight, palpitation, tachycardia, nervousness, dizziness, and insomnia. These symptoms had begun several months after a supravaginal hysterectomy 3 years previously, at which time, however, neither tube nor ovaries were disturbed. These manifestations had become increasingly severe to the time of admission. No digitalis had been given within the 6 months immediately preceding her hospitalization.

Physical examination revealed a well-nourished, well-developed woman with normally pigmented skin, heart well within normal limits of size, sounds pure, and blood pressure of 120/70. There was no evidence of organic disease in the heart or elsewhere.

The first electrocardiogram showed a sinus rate of 116 and a normal conduction time. There was a depression of the S-T segment in all three limb leads, the T-wave in Lead II was inverted, and the T-wave in CR_4 was biphasic. The next electrocardiogram (Fig. 4*B*) was taken 7 days later after 6 daily injections of 5 mg. of desoxycorticosterone acetate. The rate was 98, and the conduction time shortened to 0.18 sec. The S-T segment in all leads was less depressed than before, and the T-wave in Lead II was low but positive. The third tracing (Fig. 4*C*) was made 2 days later after 2 10-mg. doses of desoxycorticosterone acetate. The T-wave in Leads I and II and in CR_4 was then normal. The last electrocardiogram (Fig. 4*D*) was recorded 1 week after the preceding, during which time no medication had been given. No variation from Figure 4*C* was observed.

Under treatment, all of the patient's symptoms disappeared, her strength increased, and the nervousness, insomnia, and mental depression which were so prominent on admission had completely ceased to disturb her. One week after discharge from the hospital, during which time she received no medication, she was placed upon estrogenic hormone therapy, and while opportunity has not been afforded for further examination, reports from her physician indicate that she remains symptom free.

CASE 5. G. S., a woman of 21, was admitted to the hospital complaining of acute right lower quadrant pain, shifting myalgic and arthralgic pains in the arms and legs, and palpitation. The patient was small and frail, suggesting the generally hypoplastic type, although she was well proportioned with normally developed secondary sex characteristics. Her menses began at age 14 and were accustomed to recur at 33- to 45-day intervals, with 2 to 4 days of flow, the flow being scanty except for the first and sometimes the second day. Her right lower quadrant pain was at first ascribed to an appendiceal involvement, but was later thought to be of ovarian origin; no operation was performed.

Her first electrocardiogram (Fig. 5*A*) was taken after 12 days of complete

bed rest. The rate was 106. The P-R interval was 0.12 sec. The S-T segments were depressed in Leads I and II, and the T-waves were abnormally low in Lead II. In Lead III, the T-wave was inverted. The chest

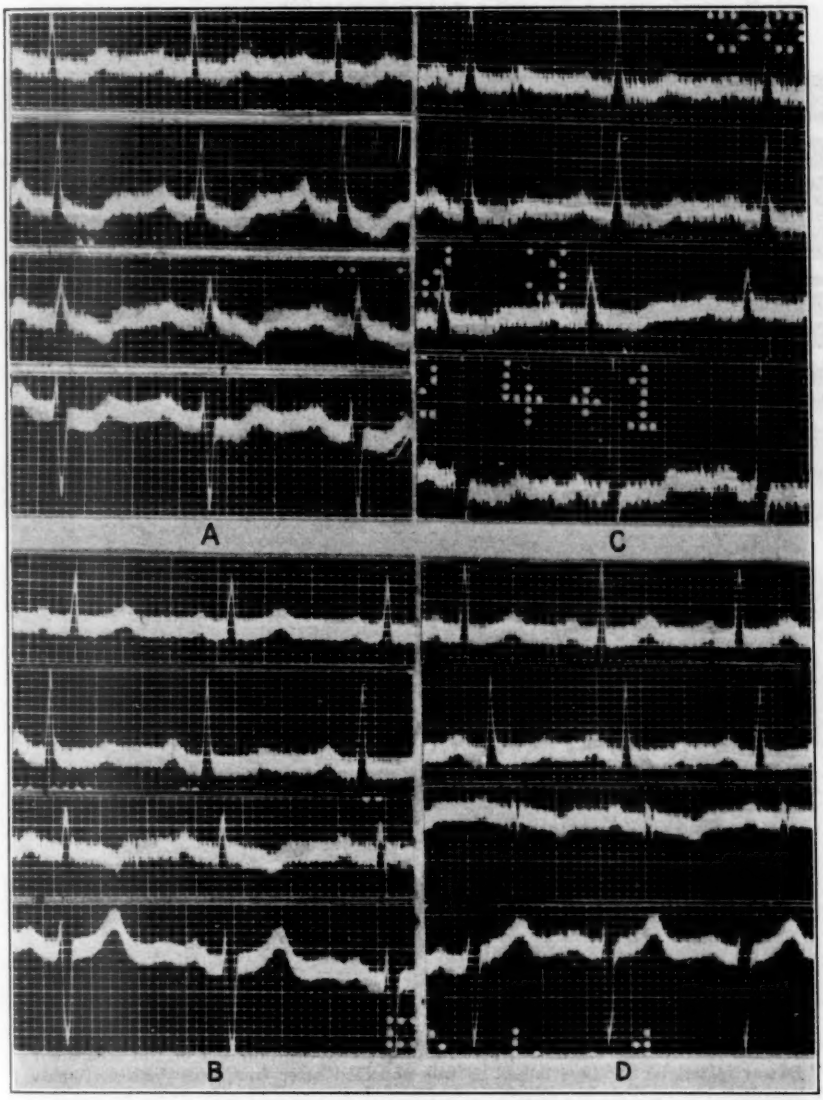

FIG. 4.—Case 4. *A* was taken before *B* after administration of desoxycorticosterone acetate. *C* was obtained after continuation of this treatment with an increased dose; *D* was taken 1 week later.

lead (CF_4) was normal. After the administration of desoxycorticosterone acetate, 5 mg. daily for 11 consecutive days, a second electrocardiogram was made (Fig. 5*B*), which showed less depression of the S-T segments and

higher T-waves than formerly. Desoxycorticosterone acetate was continued in the same does for an additional 11 days when a third tracing was obtained (Fig. 5*C*), in which practically normal S-T segments and T-waves existed. No further treatment was given for 13 days, when the electrocardiogram revealed changes noted in Figure 5*D*. The T-wave in Lead I

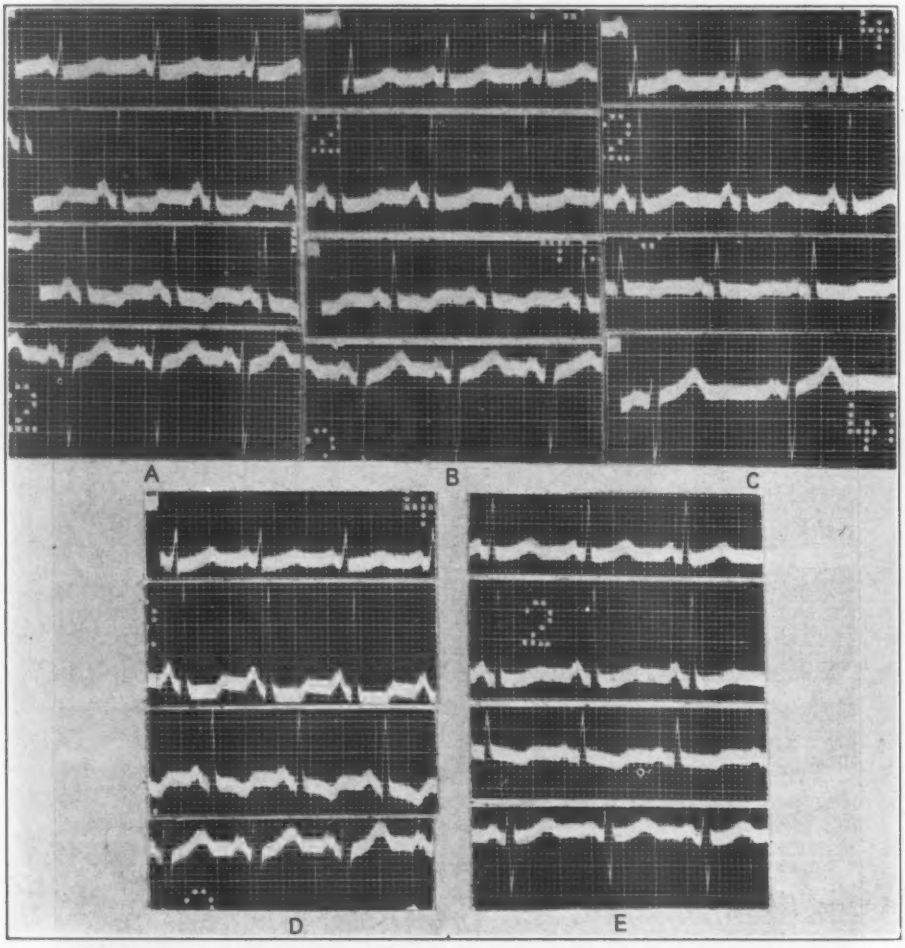

FIG. 5.—Case 5. *A* shows the electrocardiogram before, *B* after treatment with desoxycorticosterone acetate; *C* was obtained after continuation of this treatment. *D* was registered 13 days later. *E* was obtained after treatment with estrogenic hormone.

was lowered with a slight depression of the S-T segment; the S-T segment in Lead II was markedly depressed with a low deflection of the T-wave above the iso-electric line. The T-wave in Lead III was more deeply inverted than at the time of the first tracing, and the S-T in Lead CF_4 was slightly depressed. The heart rate was 115.

One week later, pregnant mare's serum (100 units, Cole and Saunders) were administered, and this dose was repeated every second day for 6 injections. Immediately following the fourth such treatment, estrogenic hormone, 10,000 international units, was given daily for 5 days. On the sixth day, an electrocardiographic tracing was made (Fig. 5*E*), which shows again changes in the direction of normal. The T-wave in Lead I is higher, and the depression of the S-T segment in Lead II is markedly diminished.

CASE 6. C. G. was admitted to the hospital for menorrhagia. The 43-year-old colored woman had had prolonged menstrual periods for the past 4 years. She was admitted to the gynecologic ward where uterine fibroids were discovered. Because of swelling of the ankles and hands, it was decided to treat her conservatively, and she was transferred to the medical ward.

Examination revealed a heart of normal size and form with a soft systolic murmur over the base. The blood pressure was 170/124. There was no evidence of an aortitis although the Wassermann reaction was 4+. All other laboratory findings were normal; there was no anemia and no evidence of congestion.

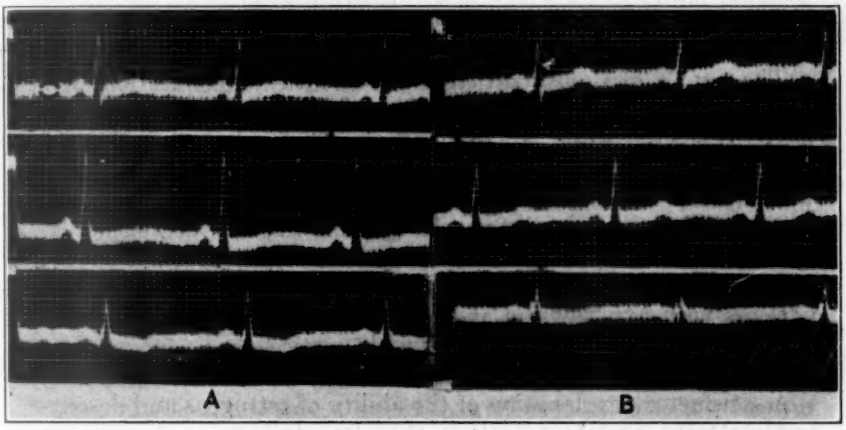

FIG. 6.—Case 6. *A* shows the electrocardiogram before, and *B* after administration of desoxycorticosterone acetate.

The electrocardiogram (Fig. 6*A*) showed a normal sinus rhythm with a normal conduction time. The T-waves in Lead I were abnormally low and were almost invisible in Lead II. Following 5 daily injections of 10 mg. of desoxycorticosterone acetate, the T-waves became completely normal (Fig. 6*B*). The blood pressure fell to 132/88, and the patient was dismissed without any symptoms. At no time had the patient received digitalis.

Discussion. The clinical findings in each of the 6 cases whose electrocardiographic findings are detailed above were unequivocally those of disturbed ovarian function. Three of these patients were of menopausal age, 2 had undergone surgical castration, and one was of a constitutionally inferior type associated with frank signs of gonadal insufficiency.

In 4 of the cases, the effect on the electrocardiogram of both desoxycorticosterone acetate and estrogenic hormone was shown to

be identical in kind, varying only in degree with the size of the dosages employed. In the fourth and sixth patients, desoxycorticosterone acetate alone was used. Improvement in the clinical symptoms followed the administration of desoxycorticosterone acetate as well as the use of the ovarian hormone. However, relief of symptoms was much more profound under estrogenic hormone therapy than it was under treatment with the adreno-cortical steroid.

The duration of improvement both in the clinical condition and in the electrocardiographic tracings varies greatly from individual to individual. As in Case 1, many patients will relapse in from 7 to 10 days after the cessation of therapy. We have followed such individuals for as long as 4 years, during which time continuous treatment has been necessary to control symptoms and electrocardiographic changes. Some patients, particularly those in the climacterium, appear to be more or less permanently relieved of circulatory and other disturbances by from one to several doses of either estrogenic or adreno-cortical steroid.

The action of desoxycorticosterone acetate in connection with ovarian dysfunction appears to have some degree of specificity. We have administered 10 mg. of desoxycorticosterone acetate for 14 days to a patient with hypopituitarism and polyglandular manifestations without any influence whatsoever on the inverted T-waves of his electrocardiogram. Again, no change following the use of similar amounts of desoxycorticosterone acetate has been noted in the inverted T-waves in Leads I and II of the electrocardiograms of patients with hypertension and evidence of left ventricular strain. According to Raab,[6] overdosage with cortico-steroid may cause changes in the electrocardiogram indicative of anoxia.

A satisfactory explanation of the ability of estrogens and desoxycorticosterone acetate to return the altered electrocardiogram to normal is fraught with some difficulties. From previous studies with the ovarian hormone, it was suggested that the vasodilating and electrolyte regulating actions of the ovarian hormone were probably responsible.[11] In view of the fact that the predominant influence of desoxycorticosterone acetate on blood-vessels is one of vasoconstriction, the vasodilation hypothesis becomes now much more difficult to defend. The effect might be an indirect one upon the ovary by way of the hypophysis, as it is known that cortical steroids do produce changes particularly in the basophile cells. This would, however, not explain the return to normal of the electrocardiogram of the two castrate patients.

Changes in calcium metabolism may play a part in the observed action, but while a number of observers are agreed upon the presence of changes in calcium metabolism in relation to the ovarian cycle in many of the lower animals,[7,17] such changes are not easily perceived in the human being[5,17] and even less well evaluated.

That sex and adreno-cortical hormones alike have a definite influence upon electrolyte and water metabolism and balance seems to be proved beyond reasonable doubt.[15,16] Thorn and Engel demonstrated that adreno-cortical hormones, desoxycorticosterone acetate among them, and the sex hormones, while differing markedly from each other in the potency and duration of their effects, all showed in common an ability to decrease the renal excretion of sodium and chloride and to raise the excretion of potassium. It is known that potassium and glycogen move into and out of muscle cells together,[1,8,10] and that the action of potassium on the heart is to some extent a specific one not shared by other skeletal muscles generally. Schumann determined the glycogen and creatine phosphate content of the heart of the male rat before and after castration and following the administration of synthetic male sex hormone.[12] After castration the amount of creatine phosphate diminished to 63% of normal, and the glycogen to 66% of normal. Administration of male sex hormone to the castrated animal augmented the amount of glycogen to 162% and returned the creatine phosphate to precastration levels. The giving of sex hormone to the normal animal increased the quantity of glycogen in the heart by approximately 100%.

The influence of desoxycorticosterone acetate on the electrocardiographic changes seen at the menopause and in other hypo-ovarian states is in part explained by what is thus far known of its gynecogenic action.[3] The progesterone-like activity of desoxycorticosterone acetate has been repeatedly observed and described following the use of proper dosages and conditions of application,[2,4,13,14] but may fail to appear when they are not present.[2,13,14] Attention should also be called to its direct estrogenic effect upon the vaginal mucous membrane of postmenopausal women.[9]

In conclusion, it is safe to assert that desoxycorticosterone acetate returns to normal the altered electrocardiograms occasionally observed in women with ovarian insufficiency in a similar way as ovarian follicular hormone. The manner in which this effect is brought about is far from settled. A vascular action, a regulatory influence upon blood and tissue electrolytes, and an interhormonal response must all be considered among the primary causes giving rise to secondary changes in the nutritional state and functional capacity of the heart.

Summary. 1. Six women with clinical manifestations of hypo-ovarianism and electrocardiographic changes, typical of such a state have been described.

2. The influence of desoxycorticosterone acetate and ovarian follicular hormone on the clinical and electrocardiographic disturbances present in each of 4 of these has been recorded and evaluated. In 2 additional individuals, changes following the administration of desoxycorticosterone acetate have been noted.

3. In each of the 4 patients to whom administered, estrogens returned the previously altered electrocardiogram to normal. Total dosages necessary for this effect varied from 14,000 to 50,000 international units.

4. In all 6 patients, the previously altered electrocardiogram reverted to normal under the influence of desoxycorticosterone acetate in total doses of 30 mg. to 60 mg. The response was equivalent in kind and in degree to that observed following the administration of ovarian follicular hormone, provided proper dosages were employed.

5. Possible explanations of this action of desoxycorticosterone acetate upon the heart are discussed. Among these we must include a direct action by way of the blood-vessels and blood and tissue electrolytes, and an indirect action by way of other endocrine glands, notably the pituitary and the gonads.

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STUDIES ON CONGESTIVE HEART FAILURE.

II. Impaired Renal Excretion of Sodium Chloride.

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The ions which predominate in the edema fluid of cardiac failure are sodium and chloride. A diet low in salt may prevent formation of edema in patients with heart failure,[7] whereas the administration of sodium salts results in oliguria and increase in weight.

These considerations indicate that retention of sodium and

chloride is involved in the accumulation of edema in patients with heart failure. The mechanism of this retention is unknown. We have attempted to ascertain whether it lies in the kidneys.

Procedure. An abundant supply of sodium and chloride was provided the kidneys of 5 patients with congestive heart failure by maintaining the concentrations of these ions in the blood at abnormally high levels for several hours following an intravenous injection of hypertonic sodium chloride solution. To prevent lowering of the serum sodium and chloride levels by dilution, an attempt was made to reëstablish cardiac compensation before the test period, in order that extracellular fluid be minimized; and ingestion of fluid was denied for 24 hours following the injection. The renal excretion of sodium and chloride was measured, and compared to the excretion in 2 subjects without heart disease who were given a similar stimulus.

For at least 2 weeks preceding the experiment all subjects, including the 2 without heart disease, were maintained on a diet containing 1 gm. of sodium chloride daily, calculated from sodium content estimated from standard food tables; 2000 calories were provided, apportioned as approximately 180 gm. of carbohydrate, 65 gm. of protein and 115 gm. of fat. The daily intake of fluid was maintained at either 1500 or 2000 cc. The output of urine, the urinary excretion of chloride, and the body weight (before the ingestion of food or fluids) were measured daily. All patients with congestive heart failure save S. DiM. had received at least 1 injection of a mercurial diuretic during the month preceding the experiments, but this measure was not employed within 2 weeks of the test. Xanthine diuretics were not used for the preceding 2 months except as indicated in Figure 1. Each of the 5 subjects with heart failure was taking digitalis at the time of the experiment. Edema, if present, was minimal. All subjects remained in bed during the first 24 hours of the experiment; only M. H. remained in bed throughout the test.

An outline of the experiment follows: *Day 1* (hours, 0 to 24): All liquids were withheld for 24 hours; the diet was deficient in fluids and contained the usual 1 gm. of salt. At time 0 hours, 400 cc. of 6% solution of sodium chloride, containing 24 gm., was injected intravenously over the course of 30 minutes. Urine was collected in 2- to 6-hour periods. Each specimen was analyzed for chloride, and in some cases for sodium and urea-plus-ammonia nitrogen (Table 2). Venous blood was usually collected at times 0, 1, and approximately 8 hours for estimation of serum chloride, and in some cases serum sodium and carbon dioxide content and blood urea nitrogen (Table 1). Venous pressure was also measured.

Day 2 (hours 24 to 48): Liquids were administered as before the test (1500 to 2000 cc.), and the diet was as usual. Urine was collected either as on Day 1, or as a pooled 24-hour specimen. A blood sample was taken at time 24 hours, previous to ingestion of food or fluids. The analyses performed on blood and urine were the same as on Day 1.

Day 3 and after: Same as Day 2.

As noted above, the usual procedure was to administer 24 gm. of sodium chloride in a single intravenous injection of 6% solution at time 0 hours. However, M. M. received a single injection of 21 gm. only, J. B. 15 gm. (250 cc.) at time 0 hours and an additional 9 gm. (150 cc.) at time 6 hours, and M. H. 24 gm. at time 0 hours and 9 gm. at time 8 hours.

During the administration of the 6% solution of sodium chloride several of the subjects complained of headache and nausea. For a few hours following the injection the patients W. D. and M. H., with severe congestive failure, exhibited orthopnea and dyspnea, and râles were heard in the lungs. All of the patients complained of thirst; 2 were allowed a few cubic centimeters of crushed ice during the first day. Albuminuria, when present previous to the injection of salt, was not increased by it. A week or more

after the experiment a mercurial diuretic was given to all the patients with cardiac failure, except in the case of the first period of N. J., when abdominal paracentesis was performed, in order to free them of edema accumulated during the test.

TABLE 1.—VENOUS PRESSURE AND CHEMICAL ANALYSES ON BLOOD BEFORE AND AFTER INTRAVENOUS INFUSION OF SODIUM CHLORIDE (21 TO 33 GRAMS).

Subject, date, diagnosis.	Time after injection of salt (hrs.).	Serum sodium (m.eq. per liter).	Serum chloride (m.eq. per liter).	Serum carbon dioxide content (mM. per liter).	Blood urea nitrogen (mg. per 100 cc.).	Venous pressure (mm.).
Case 1 (G. S.)	0	..	97	..	..	60
January, 1940	1	..	116			
Bronchial asthma	10	..	114			
	24	..	111			
	48	..	105			
	120	..	100			
Case 2 (M. M.)	0	142	108	..	16.5	105
October, 1940	1	153	119	..	15.6	105
Hypoproteinemia	12	150	119	..	21.1	94
	24	151	117	..	18.8	111
	48	144	112			
	72	..	109			
	120	..	107			
Case 3 (S. DiM.)	0	..	97	..	..	127
February, 1940	8	..	113			
Mild heart failure	24	..	111			
	72	..	100			
Case 4 (W. D.)	0	136	98	..	..	225
June, 1940	1	151	111			
Severe heart failure	9	148	109			
	24	149	108	..	..	231
	72	137	97			
February, 1941	0	136	97	..	18.3	205
	1	146	107	..	..	210
	9	143	107	..	18.6	221
	24	146	109	..	19.3	198
	48	144	104	..	21.6	220
Case 5 (M. H.)	0	137	94	33.1	6.2	125
June, 1941	1	148	111	29.8	..	95
Severe heart failure	9*	153*	118*	27.0*		
	24	155	117	29.6	8.6	175
	48	150	110	30.6	9.2	150
	72	143	106	28.3	9.1	172
	120	137	103	29.2	..	172
Case 6 (J. B.)	0	..	107	..	..	115
November, 1940	6	..	109	..	..	167
Severe heart failure	9*	..	115*			
	24	..	112	..	..	158
	72	..	105			
	96	..	..	..	..	193
	168	..	103			
Case 7 (N. J.)	0	..	99	..	..	245
January, 1940	1	..	112			
Severe heart failure;	24	..	107			
renal disease	96	..	103			
	192	..	100			
March, 1940	0	..	97	..	..	61
	1	..	111			
	9	..	111			
	24	..	112			
	48	..	110			
	120	..	101			

* Following second injection of 6% sodium chloride; see text under "Procedure."

Analytical Methods. Serum chloride was estimated by the method of Van Slyke.[9a]† The Volhard-Arnold procedure[4] was used to measure urinary

† The normal values obtained by this method range from 99 to 108 milliequivalents per liter (average about 102). The chloride content of the serum of patients taking such salt-poor diets was usually found to be lower than this; 96 to 100 milliequivalents. The initial values of 1 control and all but 2 cardiac patients were in this range; the other control and 1 cardiac exhibited high initial values.

chloride, with occasional checks by the titrimetric silver iodate method of Sendroy.[8] Urinary sodium was estimated by the technique of Butler and Tuthill,[1] as described for urines of "ordinary sodium content." Butler and Tuthill's method, modified by Consolazio and Dill,[2] was also used for the measurement of serum sodium. Whole blood and urine were analyzed for

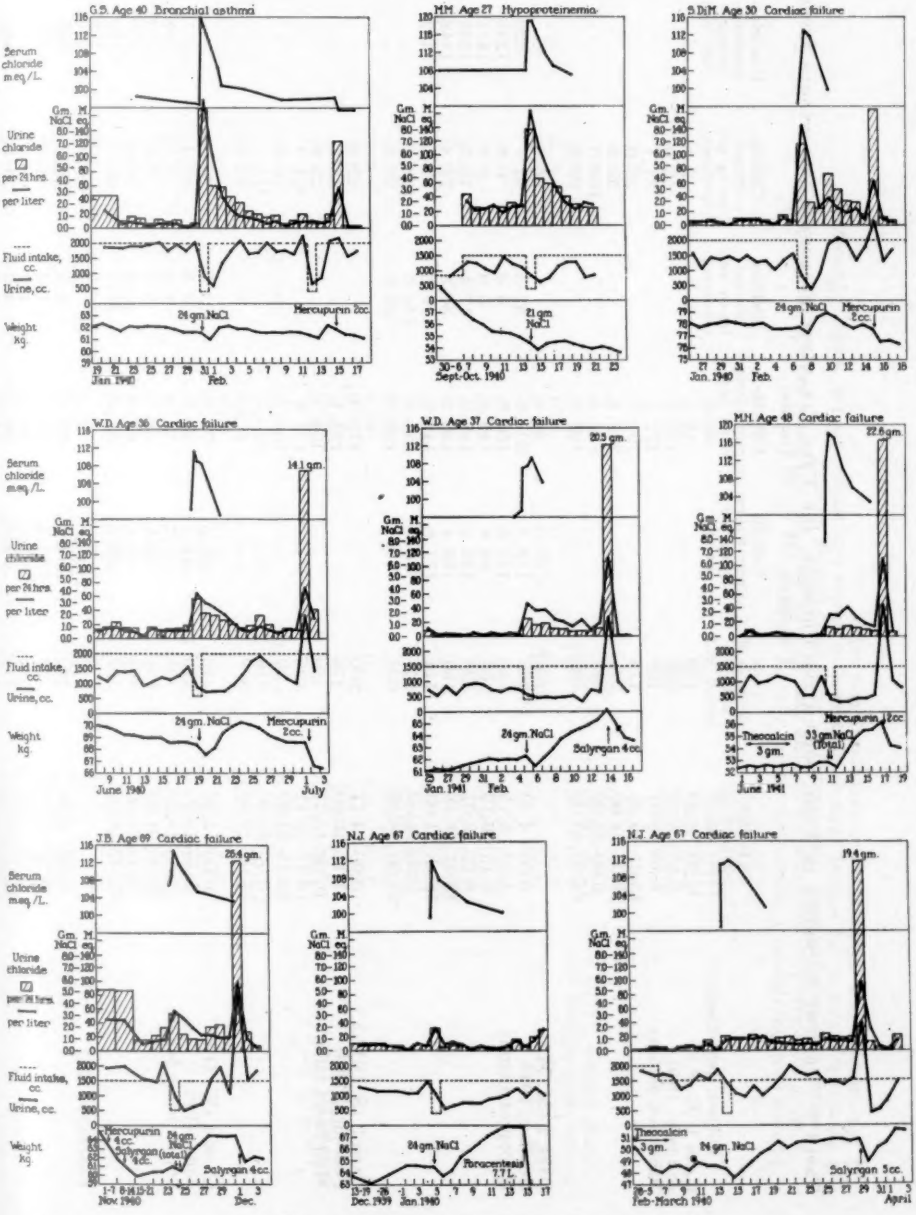

FIG. 1.—Data on all patients studied.

TABLE 2.—URINARY EXCRETION OF UREA, SODIUM AND CHLORIDE, AND UREA CLEARANCE FOLLOWING INTRAVENOUS INFUSION OF SODIUM CHLORIDE (21 TO 33 GRAMS).

Subject, date, diagnosis.	Time after injection of salt (hrs.: min.).	Volume of urine for period (cc.).	Sodium concentration (m.eq. per liter).	Chloride concentration (m.eq. per liter).	Sodium content (m.eq. per specimen).	Chloride content (m.eq. per specimen).	Urea-plus-ammonia nitrogen (mg. %).	Urea-plus-ammonia clearance (% of normal).
CASE 1 (G. S.)	0:00– 0:50	110	..	31.1	..	3.4		
January, 1940	0:50– 6:58	296	..	178.9	..	53.0		
Bronchial asthma	6:58–13:01	198	..	172.1	..	34.1		
	13:01–19:00	120	..	191.8	..	23.0		
	19:00–24:00	204	..	272.1	..	55.5		
	0:00–24:00	*928*	..	*182.1*	..	*169.0*		
	24:00–48:00	*592*	..	*102.9*	..	*60.9*		
CASE 2 (M. M.)	..	*1120**	*<20.0*	*25.6*	..	*28.7*	..	*88.6**
October, 1940	0:00– 4:20	302	173.3	207.8	52.3	62.7	520	60.2
Hypoproteinemia	4:20– 6:15	44	121.5	154.9	5.3	6.8	1245	95.8
	6:15– 9:15	63	93.8	140.2	5.9	8.8	1411	76.8
	9:15–13:01	128	136.2	146.0	17.4	18.7	1385	95.8
	13:01–18:48	190	180.4	130.5	34.3	24.8	1348	91.7
	18:48–24:00	114	171.6	142.6	19.6	16.3	1462	91.4
	0:00–24:00	*841*	*160.2*	*164.3*	*134.8*	*138.1*	..	*85.3*
	24:00–48:00	*605*	*110.1*	*109.6*	*66.6*	*66.3*	..	*110.5*
CASE 3 (S. DiM.)	0:00– 4:11	200	..	112.9	..	22.6		
February, 1940	4:11–10:09	275	..	128.1	..	35.2		
Mild heart failure	10:09–16:11	180	..	164.2	..	29.6		
	16:11–22:11	125	..	173.8	..	21.7		
	22:11–24:00	36	..	156.7	..	5.6		
	0:00–24:00	*816*	..	*140.5*	..	*114.7*		
	24:00–48:00	*372*	..	*87.4*	..	*32.5*		
CASE 4 (W. D.)	0:00– 5:56	410	56.5	70.6	23.2	28.9		
June, 1940	5:56–12:00	210	41.9	59.0	8.8	12.4		
Severe heart failure	12:00–18:00	138	57.7	51.3	8.0	7.1		
	18:00–24:00	134	39.6	58.1	5.3	7.8		
	0:00–24:00	*892*	*50.8*	*63.0*	*45.3*	*56.2*		
	24:00–48:00	*715*	*38.7*	*51.3*	*27.7*	*36.7*		
February, 1941	..	*710**	*<20.0*	*2.7*	..	*1.9*	..	*84**
	0:00– 3:54	152	53.6	79.0	8.2	12.0	862	73
	3:54– 5:33	62	<20.0	29.2	<1.2	1.8	1171	91
	5:33–11:01	95	22.0	31.0	2.1	2.9	1333	73
	11:01–16:29	112	29.4	29.2	3.3	3.3	1464	86
	16:29–24:00	118	21.6	44.8	2.6	5.3	1436	72
	0:00–24:00	*539*	*<32.3*	*46.9*	*<17.4*	*25.3*	..	*79*
	24:00–48:00	*443*	*<20.0*	*30.7*	*<8.9*	*13.6*	..	*84*
Severe heart failure	4:01– 7:58	80	<20.0	21.5	..	1.7	1026	184
	7:58– 12:02	80†	29.3†	34.2†	2.3†	2.7†	1179†	214†
	12:02– 16:02	47	<20.0	27.4	..	1.3	1275	129

	5:33–11:01	95	22.0	31.0	2.1	2.9	1333	73
	11:01–16:29	112	29.4	29.2	3.3	3.3	1464	86
	16:29–24:00	118	21.6	44.8	2.6	5.3	1436	72
	0:00–24:00	*539*	*<32.3*	*46.9*	*<17.4*	*25.3*	..	*29*
	24:00–48:00	*432*	*<20.0*	*[illegible]*	..	*[illegible]*	*[illegible]*	*[illegible]*
Severe heart failure	4:01– 7:58	80	<20.0	21.5	..	1.7	1026	184
	7:58– 12:02	80†	29.3†	34.2†	2.3†	2.7†	1179†	214†
	12:02– 16:02	47	<20.0	27.4	..	1.3	1275	129
	16:02– 20:00	43	<20.0	17.8	..	0.8	1219	118
	20:00– 24:00	44	<20.0	23.2	..	1.0	1340	131
	0:00– 24:00	*420*	..	*29.8*	..	*12.5*	..	*151*
	24:00– 27:58	62	<20.0	23.3	..	1.4	1272	149
	27:58– 31:59	51	<20.0	26.7	..	1.4	1381	145
	31:59– 35:59	65	<20.0	26.7	..	1.7	1464	174
	35:59– 39:59	62	<20.0	25.1	..	1.6	1574	171
	39:59– 44:00	46	<20.0	31.8	..	1.5	1431	134
	44:00– 48:00	45	<20.0	48.9	..	2.2	1440	134
	24:00– 48:00	*331*	*<20.0*	*29.4*	..	*9.8*	..	*151*
	48:00– 72:00	*349*	*<20.0*	*40.2*	..	*14.0*		
	72:00– 96:00	*453*	*<20.0*	*26.7*	..	*12.1*		
	96:00–120:00	*447*	*<20.0*	*19.8*	..	*8.9*		
	120:00–144:00	*550*	*<20.0*	*13.7*	..	*7.5*		
	144:00–168:00	*3560‡*	*86.2‡*	*108.8‡*	*306.9‡*	*387.3‡*		
CASE 6 (J. B.)	0:00– 4:55	157	..	29.8	..	4.7		
November, 1940	4:55– 5:15	61	..	36.6	..	2.2		
Severe heart failure	5:15– 7:10	76†	..	53.4†	..	4.1†		
	7:10– 9:40	94	..	43.4	..	4.1		
	9:40–12:25	126	..	60.2	..	7.6		
	12:25–18:48	205	..	71.8	..	14.7		
	18:48–20:40	63	..	98.8	..	6.2		
	20:40–21:55	58	..	86.4	..	5.0		
	21:55–24:00	117	..	58.5	..	6.8		
	0:00–24:00	*957*	..	*57.9*	..	*55.4*		
	24:00–48:00	*504*	..	*47.6*	..	*24.0*		
CASE 7 (N. J.)	0:00– 3:00	260	..	50.3	..	13.1		
January, 1940	3:00– 9:00	308	..	28.4	..	8.7		
Severe heart failure;	9:00–15:00	228	..	23.3	..	5.3		
renal disease	15:00–24:00	238	..	19.8	..	4.7		
	0:00–24:00	*1034*	..	*30.8*	..	*31.8*		
	24:00–48:00	*555*	..	*8.6*	..	*4.8*		
March, 1940	0:00– 5:58	447	..	18.5	..	8.3		
	5:58–11:30	350	..	17.8	..	6.2		
	11:30–17:55	296	..	4.4	..	1.3		
	17:55–24:00	340	..	14.0	..	4.8		
	0:00–24:00	*1433*	..	*14.4*	..	*20.6*		
	24:00–48:00	*1064*	..	*17.0*	..	*18.1*		

Figures in italics represent summaries and averages for 24 hours.
"<20.0" indicates that concentration was less than 20 m.eq. per liter, and hence was not accurately measured.
* Average clearance and total urine volume for 24 hours preceding infusion.
† Second injection of 6% sodium chloride administered during this period; see text under "Procedure."
‡ Mercupurin, 2 cc. administered intravenously this day.

urea-plus-ammonia nitrogen by the method of Van Slyke and Kugel,[9b,10] and the urea-plus-ammonia clearance was calculated from these data by the formulæ of Møller, McIntosh, and Van Slyke,[6] correcting urine flow for size on the basis of height.[5] Serum carbon dioxide content was measured by the method of Van Slyke and Neill.[11] Venous pressure was measured by the direct method and is expressed as millimeters of 0.8% solution of sodium chloride; heart level was assumed to be 5 cm. below the sternomanubrial junction, with the patient in the supine position.

Case Reports. The 2 control subjects, G. S. and M. M. (Cases 1 and 2) suffered from bronchial asthma and hypoproteinemia respectively; the renal function of neither was impaired. G. S. was chosen as a relatively normal individual; M. M. because of the presence of edema not due to cardiac or renal diseases. Of the 5 patients with heart disease, 3 (S. DiM., W. D. and M. H., Cases 3, 4 and 5) had rheumatic heart disease with no impairment of renal function and no evidence of active rheumatic fever. Two patients (J. B. and N. J., Cases 6 and 7) had arteriosclerotic heart disease; there was evidence of impairment of renal function in the latter.

Case 1.—G. S., male, age 40, height 175 cm., had suffered from mild bronchial asthma, unaccompanied by cardiovascular or renal complications. Urea clearance was 80% of normal.

Case 2.—M. M., female, age 29, height 157 cm., had moderate anasarca due to hypoproteinemia, possibly complicating sprue. The edema was of 11 years' duration and had responded in the past to mercurial diuretics. Plasma albumin concentration was 1.8 and globulin 1.6 gm. per 100 cc. Her serum chloride concentration previous to the test was always higher than normal, ranging from 107 to 110 m.eq. per liter, and her serum carbon dioxide content was 26.4 mM. per liter. There was no evidence of cardiac or renal lesions. The urea clearance averaged 100% of normal. The urine contained no protein or formed elements, and had a maximum specific gravity of 1.026. Minimal edema was present at the time of her test, which was performed at a time when, apparently in association with the recent institution of the low salt diet, a diuresis was in progress.

Case 3.—S. DiM., female, age 30, height 157 cm., suffered from rheumatic heart disease with mitral stenosis. She had complained of exertional dyspnea and slight edema intermittently for 3 years. Her blood pressure was 130/80. Urea clearance was 90% of normal, and the maximum urinary specific gravity 1.026. There was no evidence of heart failure at the time of her test.

Case 4.—W. D., male, age 42, height 166 cm., suffered from rheumatic heart disease, with mitral stenosis, aortic insufficiency, and auricular fibrillation. Symptoms and signs of severe congestive failure appeared 1 year before the test of June, 1940. Blood pressure was 160/80 in June, 1940, and 140/70 in February, 1941. There was slight albuminuria (1+). In May, 1940, the plasma albumin measured 3.3 and the globulin 3 gm. per 100 cc.; in April, 1941, these figures were 4.1 gm. and 2.9. The urea clearance averaged 90% of normal; and the maximum urinary specific gravity in June, 1941, was 1.024. Even with rest and diuretics edema was not completely controlled. Slight jaundice was frequently observed. At the time of each of the two tests performed on this patient, in June, 1940, and February, 1941, slight ascites, enlargement of the liver and orthopnea were noted, decompensation being more marked when the first was done.

Case 5.—M. H., female, age 48, height 154 cm., suffered from rheumatic heart disease, with auricular fibrillation, mitral stenosis, and tricuspid insufficiency. Menopause occurred 5 years before admission. She had noted symptoms and signs of heart failure for 12 years, and edema, not satisfactorily controlled by digitalis or mercurial diuretics, was constant for 5 years. Blood pressure was 132/80. The urine contained albumin

(1+). The maximum specific gravity of the urine was 1.024. The plasma albumin concentration was 3.9 and the globulin 3 gm. per 100 cc. Slight orthopnea persisted at the time of the test, there was a small hydrothorax, and her liver was enlarged.

CASE 6.—J. B., male, age 69, height 165 cm., suffered from arteriosclerotic heart disease, with auricular fibrillation. Symptoms of severe congestive failure had been present for 3 years. Blood pressure was 132/84. The urine contained albumin (2+) and a few red blood cells. The plasma albumin was 3.6 and the globulin 2.8 gm. per 100 cc. The blood non-protein nitrogen was 32 mg. per 100 cc.; the urea clearance, measured 2 years before the test, was 70% of normal, the maximum specific gravity of the urine was not determined. Despite use of diuretics, orthopnea and edema were observed at times in the hospital. There was no edema at the time of his test, but his liver was enlarged.

CASE 7.—N. J., male, age 67, height 160 cm., suffered from arteriosclerotic heart disease with aortic insufficiency and auricular fibrillation. Symptoms and signs of severe congestive failure had been present for 3 years. Blood pressure was 142/80. The plasma albumin in July, 1940, was 3.7 and the globulin 3.2 gm. per 100 cc. Urine contained albumin (1+). The urea clearance was 37% of normal in October, 1939, and again in February, 1940; the blood urea nitrogen on these occasions was 23 and 27 mg. per 100 cc. Edema was difficult to control. Ascites and edema were present at the time of the first test performed; compensation had been partially restored at the time of the second. The patient died in uremia in January, 1941. At autopsy the kidneys showed only moderate arteriosclerotic changes.

Results. During the 24 hours following the injection of salt, the renal excretion of sodium and chloride ions in the 4 patients with severe cardiac disease was not more than 30% of that observed in the 2 control subjects. In respect to chloride the urine of the patients with severe heart disease was always hypotonic when compared with the serum.

The changes in the concentrations of chloride and sodium in the serum are described in Table 1. The degree of elevation produced varied from subject to subject; however, 24 hours after the injection the serum chloride and, when determined, sodium concentrations in all subjects proved to be at levels higher than normal.

The urinary excretion of these ions, and the urea clearance values, are given in Table 2. More extended data on urinary chloride are presented in the graphic analyses (Fig. 1). The 2 control subjects (Cases 1 and 2) achieved urinary chloride concentrations of 182 and 164 m.eq. per liter during the 24 hours following the injection of salt; the total 24-hour excretion of chloride was 169 and 138 m.eq. Thus, hypoproteinemia of a degree sufficient to cause edema did not prevent Case 2 from excreting salt approximately as efficiently as did the other control subject, Case 1. The patient convalescent from mild cardiac failure (Case 3) achieved a concentration of 140 m.eq. of chloride per liter, and excreted 115 m.eq. in 24 hours. The three tests on the 2 patients recovering from severe cardiac failure who exhibited normal or elevated urea clearance (Cases 4 and 5) revealed 24-hour chloride concentrations of 63, 47 and 30 m.eq. per liter; the total 24-hour outputs of chloride were

56, 25 and 12 m.eq. Case 6, the patient recovering from severe heart failure whose renal function was not recently investigated, excreted chloride in a concentration of 58 m.eq. per liter, the 24-hour output of chloride being 55 m.eq. Finally, Case 7, who, in addition to suffering from severe cardiac disease showed evidence of impaired renal function, on 2 different occasions excreted chloride in a concentration of 31 and 14 m.eq. per liter; the total 24-hour outputs were 32 and 21 m.eq. The concentration of sodium in the urine of the patients in whom the measurement was made paralleled that of chloride.

Chloride clearances were calculated from the date presented in Tables 1 and 2 and from additional data not included therein. For a given subject, there was noted a tendency for the clearance to vary directly with the serum chloride level and the urine volume. There were numerous marked deviations from these trends, however, particularly in the patients with heart disease. The averages of the chloride clearances* for each patient during those periods when the falling curve of the serum chloride level was in the range 108 to 111 m.eq. per liter inclusive follow: Case 1, 0.93 cc. of serum per minute; Case 2, 0.40 cc.; Case 3, 0.47 cc.; Case 4 (June, 1940), 0.24 cc.; Case 4 (February, 1941), 0.13 cc.; Case 5, 0.11 cc.; Case 6, 0.20 cc.; Case 7 (January, 1940), 0.16 cc.; and Case 7 (March, 1940), 0.15 cc. of serum per minute. Case 5 whose chloride clearance throughout the test was the lowest observed in any of the patients also showed the lowest urine flow.

The administration of mercurial diuretics to patients with cardiac failure may occasion excretion of sodium and chloride in concentrations exceeding those observed following the intravenous administration of sodium chloride; this fact is demonstrated by the data on Cases 4, 5, 6 and 7, presented in Table 2 and Figure 1. For example, Case 5, following the injection of sodium chloride, excreted in 24 hours 420 cc. of urine with a chloride concentration of 30 m.eq. per liter; following the intravenous administration of 2 cc. of mercupurin, the 24-hour excretion was 3560 cc. of urine with a chloride concentration of 109 m.eq. per liter. For Case 7, whose urea clearance was 37% of normal, the intravenous injection of 24 gm. of salt occasioned the excretion of 1433 cc. of urine with a chloride concentration of 14 m.eq. per liter. Two weeks later, after intravenous administration of 5 cc. of salyrgan the 24-hour output was 3439 cc. of urine with a chloride content of 96 m.eq. per liter. This did not occur in the cases of a control subject (Case 1) and the patient with mild heart failure (Case 3) (Fig. 1).

* The amount of serum cleared of chloride by the kidneys was calculated by the formula: $\frac{U}{B} \times Vc$, when U and B are the urine and serum concentrations of chloride respectively, and Vc is the urine flow per minute, corrected for size on the basis of height.[5,6]

Discussion. The filtration-reabsorption theory of renal physiology offers two mechanisms which might occasion the impaired excretion of sodium chloride observed in our patients with congestive heart failure. First, the volume of glomerular filtrate may have been diminished below normal, the renal tubules consequently reabsorbing a greater proportion of filtered sodium and chloride without actually increasing their rate of reabsorption of these ions. The fact that in Cases 4 and 5, with severe heart failure, the urea clearance remained at its previous normal or high level during the test suggests that glomerular filtration was not depressed after the injection of salt.

The second, more likely explanation for the diminished urinary excretion of sodium chloride is an increased rate of tubular reabsorption of these ions, the result of circulatory changes in the kidney or of hormonal influences upon the renal tubular cells. Thus, increased venous pressure or renal anoxemia may perhaps stimulate the reabsorption of salt by the tubules. Or the increased tubular reabsorption may be effected by an endocrine mechanism, possibly involving the adrenal cortex,[3] set in motion by heart disease or by therapeutic measures instituted during the treatment of heart disease. An abnormally low rate of excretion of ingested sodium chloride has also been observed in patients with diabetes insipidus.[12]

Our data do not indicate whether the observed abnormality involved primarily the excretion of *both* the sodium and the chloride ion, or merely one of the pair. The greater facility with which chloride can be measured explains why the majority of our information is on that ion rather than sodium.

If the retention of ingested salt observed clinically in patients with heart failure is to be explained as primarily due to failure of the kidney to excrete sodium and chloride in normal amounts, an explanation must also be offered for the fact that the concentrations of these ions in the serum of patients with congestive heart failure are not found elevated. Water must be secondarily retained by the kidney, in sufficient quantities to adjust the concentrations of sodium and chloride to the normal range. Instead of salt being excreted in a normal manner, salt, and therefore water are retained; this mechanism was certainly active in our patients with congestive heart failure during the days following an injection of salt, as indicated by the fall in serum electrolyte levels, the increase in weight, and the fall in urine volume.

Summary. 1. In 4 patients convalescent from severe congestive heart failure there was found an impairment of the ability of the kidney to excrete sodium and chloride, (as compared to 2 subjects without heart disease), when the concentration of these ions in the serum was experimentally elevated above normal.

2. Mercurial diuretics increased the excretion of sodium and chloride by these same subjects.

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STUDIES ON "ESSENTIAL" HYPERTENSION.

IV. Early Arterial Hypertension.

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Studies of patients exhibiting so-called "essential" arterial hypertension have been rewarding in that the coëxistence of a variety of abnormalities has suggested that this condition is not a single disease.[6a] Only those patients have been studied in whom the date of onset of the elevated blood pressure was known. When certain other circumstances occurring at or before the time of onset of the condition were also known, it was sometimes possible to arrive at an opinion regarding the mode of onset, some of the precipitating factors, and the subsequent development of events.

Because facts about the early stages of arterial hypertension appeared important, a group of cases exhibiting slight elevation of blood pressure of short duration were investigated in the hope that some information bearing on the mode of onset of hypertension might be made available. Disturbances of the nervous system and the genito-urinary tract were especially studied in an attempt to ascertain their relation to elevation of the blood pressure.

Material and Methods. Cases were selected when the following conditions were observed: *a*, systolic blood pressure of more than 150 mm. Hg on at least 3 occasions, but which was usually between 140 and 150; *b*, diastolic blood pressure of more than 85 mm. Hg on at least 3 occasions, but which was usually less than 100; and, *c*, the discovery of hypertension on routine examination. Cases in younger subjects were studied, excluding patients with general arteriosclerosis. All cases came because of elevation of the blood pressure, and none because associated disturbances had been discovered.

The usual examinations were always made, some with the view of eliciting

etiologic factors, and others with establishing the existence of the effects of the elevated blood pressure. The former include: a detailed history; physical examination; cursory psychologic examination; studies of the genito-urinary tract, with bacteriologic cultures of the urine, pyelograms after intravenous injection of diodrast, and, when necessary, cystoscopic examination and retrograde pyelography; estimation of the basal metabolic rate; and Roentgen ray photographs of the skull and larger arteries. The latter include: examination of the ocular fundi, physical examination, taking an electrocardiogram and Roentgen ray photographs of the heart, studies of the function of the kidneys (the ability of the kidneys to concentrate urine and the clearance of urea), and measurements of the blood pressure under various conditions.

There were 50 cases in this group; 36 males, 14 females. Thirty-five were under 30 years of age at the onset of the disease, and 15 were under 20. All exhibited elevation of the systolic pressure. The diastolic pressure in all but 9 was on occasions 90 mm. Hg or more. Cases were classified according to the plan proposed by Schroeder and Steele.[6a] Thirty-seven exhibited lesions of the kidneys, of varying degrees of severity, and were therefore thought to be suffering from "renal" hypertension. In 13 there was no obvious disease of the genito-urinary tract.

Renal function was normal in every case. Basal metabolic rates were not altered. In no instance was the shadow of the heart in Roentgen ray photographs enlarged. Electrocardiograms in a few cases exhibited abnormalities of slight degree. The ocular fundi were essentially normal. Measurements of the blood pressure were significant in that 25 at times exhibited pulse pressures increased out of proportion to the elevation of systolic pressure; diastolic pressures were accordingly often low.

"Renal" Hypertension. Of 37 cases exhibiting lesions of the urinary organs, ureteral obstruction was present in 23, obstruction with infection in 4, infection in 7, and congenital abnormalities in 3 (Table 1). The relation of infection in the urine to the onset of hypertension was fairly well demonstrated in 1 (Case 14). Operative removal of an obstruction at the uretero-pelvic junction in 1 instance resulted in a fall of the blood pressure to normal, although the effect was, of course, slight (Case 10). That mild hypertension occurred as a result of infection (Case 12) and of urinary obstruction (Case 1) was often clear. Only 4 have subsequently developed persistent hypertension. Similar findings at the onset of the disease in other patients exhibiting severe arterial hypertension offer evidence that these individuals are "potentially" hypertensive, and may become permanently so later on.

"Nervous" Hypertension. Thirteen patients exhibited elevation of the blood pressure without organic renal disease. Eleven suffered from psychologic disturbances (Table 2). In 5 psychoneuroses were of sufficient severity to interfere with normal existence (Cases 44 and 45); in 2, such disturbances were not evident on routine examination, but signs of the "diencephalic syndrome"[4] were present.

Environmental influences were contributory in 7 cases. Ten complained of headache. One had been treated for a benign tumor of the brain, and 1 suffered from neurosyphilis.

An attempt was made to examine separately some of the clinical phenomena which have been considered to be concerned with the existence of hypertension. Because there are often abnormal family histories, various disturbances of the kidneys and the nervous system, and abnormal reactions to environmental influences, these were made the basis of analysis.

The Various Factors Associated With Hypertension. Two factors at least are probably necessary for the occurrence of arterial hypertension; 1, a *constitutional* one, includes a familial tendency to the disease and the patient's general physical and psychologic characteristics, especially those of his nervous system; 2, a *morphologic* one, applies to the existence of renal disease, or renal arteriosclerosis, or the development of nervous tension resulting from environmental influences (in most cases there was evidence of both); 3, a *precipitating* factor, is sometimes exactly known.

Constitutional Component. There existed in 34 of 41 cases a history of arterial hypertension in a member of the family one or two generations before that of the patient, and in 5 others in a member of the same generation. In 7 there was hypertension in the families of both parents. In addition the temperament of almost every patient could be characterized either by the expression, "high strung" or "unstable" to some degree, although the derangement was often well controlled. The diencephalic syndrome was prominent in half. Although in many cases environmental influences were unfavorable, the resultant mental conflict was usually excessive. The level of intelligence of the younger individuals appeared to be above the average; but their reactions to emotional stimuli were often extreme. Emotional instability of some degree occurred in 44 of the 50 patients. Flushing with excitement was common. Most complained of excessive perspiration, and their extremities were usually cold. Many were given to worrying, and became irritable when their affairs were not progressing favorably. These symptoms, it seemed, usually antedated the onset of hypertension, sometimes becoming more prominent as the blood pressure rose.

Morphologic Component. In a majority of patients (37) renal disease of various sorts was found to exist in combination with elements of the constitutional factor (Table 1). Often it also occurred with dysfunction of the nervous system (Case 31), but occasionally alone (Case 24). Relatively severe renal disease as estimated anatomically was associated with very little nervous instability (Cases 1, 12, 14); similarly, slight renal disease with more pronounced nervous disturbance have been found together (Case 26). There was no relation, therefore, between the severity of renal affections and the height of the blood pressure.

TABLE 1.—MILD ARTERIAL HYPERTENSION ASSOCIATED WITH RENAL DISEASE.

Case No.	Name.	Sex.	Age at onset and duration of hypertension (yrs.).		Extremes of blood pressure. Highest (mm. Hg).	Lowest (mm Hg).	Constitutional components. Family history.*	Emotional instability.†	Physical signs.‡	Morphologic component.	Albumin in urine.§	Onset with.
1	H. K.	M	16	5	160/110	124/78	M	++	++++	Horseshoe kidney ?	0	
2	A. L.	M	17	2	160/90	134/70	S	+++	+++	Sl. rt. hydronephrosis	0	
3	E. B.	M	16	6	180/80	136/60	M	+	+	Bilat. hydronephrosis	0	
4	B. B.	M	20	3	180/104	142/88	S	0	+	Sl. bilateral hydronephrosis	0	
5	P. L.	M	22	2	156/92	132/78	M+	++	+++	Sl. rt. hydronephrosis	0	
6	C. H.	M	18	4	150/70	132/86	S	+++	+++	Bilat. hydronephrosis	0	
7	F. G.	M	12	10	180/100	144/68	M+	+	++	Rt. hydronephrosis		
8	P. H.	M	19	2	162/90	126/54	0	++	++	Double ureters and pelves	0	
9	G. H.	M	17	2	150/90	132/74	M	+	0	Rt. renal ptosis	±	
10	J. P.	M	17	3	162/68	144/92	M	+++	++	Marked rt. hydronephrosis		
11	H. B.	M	22	2	180/98	144/85	—	++	++++	Blunting of renal calyces	0	
12	L. W.	M	14	5	182/110	136/60	F M	+	+++	Bilat. hydronephrosis ?	+	
13	J H.	M	21	2	160/90	140/82	S	+++	++++	Right hydronephrosis	±	
14	H. M.	M	16	1	170/94	122/50	F H	+	+++	Right pyelonephritis ?	±	Infection.
15	B. S.	M	16	3	166/70	134/90	S	++	++	Dilatation of ureters	+	Infection.
16	C. J.	M	25	1	162/92	150/70	F	++++	+	Absent left kidney ?	0	Psychoneurosis.
17	C. W.	M	22	1	180/88	138/80	(F)	++	0	Dilatation of ureter, infection	0	
18	J. J.	M	25	1	164/100	132/70	M	++	++	Right hydronephrosis	0	
19	P. Z.	M	29	4	150/90	122/60	?	+++	+++	Sl. left hydronephrosis	0	Anxiety.
20	M. S.	M	33	3	158/110	130/90	M	+++	++	Sl. right hydronephrosis	±	
21	F. R.	M	28	1	164/94	135/80	M+ F+	++	+	Pyelonephritis, old	0	
22	H. M.	M	29	8	160/100	138/80	M+ F+	0	+++	Sl. right hydronephrosis	0	
23	M. M.	M	34	6	170/90	132/70	F (M)++	0	+	Pyuria ? infection	±	
24	M. W.	M	32	7	170/110	134/90	M	+	0	Bilateral hydronephrosis	0	
25	P. F.	M	36	9	150/90	126/80	M	0	+	Pyuria	0	
26	D. R.	F	30	4	174/106	140/82	M	++++	++++	Angulation of ureters	±	Worry over disease.
27	S. S.	F	34	4	164/110	122/88	M++	++	+++	Sl. right hydronephrosis	0	
28	J. H.	F	50	13	178/100	140/80	M	+	+++	Angulation, right ureter	0	Husband's death.
29	P. M.	F	47	7	184/94	140/70	M	++	+++	Rt. ptosis and hydronephrosis	0	Economic worry.
30	R. M.	F	53	7	184/116	134/90	M	++++	+++	Right ptosis and hydronephrosis, infection	+	Infection?
31	G. W.	F	36	3	162/100	142/80	M	++++	++++	Rt. kid., poor func., hydronephrosis	+	Preg. and emot. crisis.
32	G. F.	F	23	3	182/110	124/74	F+	++	++	Bilat. "embryonic" kidneys	±	
33	V. T.	F	40	1	150/90	128/84	—	+++	++++	Sl. bilateral hydronephrosis	0	Worry, child ill.
34	L. H.	M	25	2	160/90	128/70	(M)	++	+	Left hydronephrosis	0	
35	V. W.	M	17	1	160/88	128/64	?	++++	+++	Infection ?	+	
36	L. B.	M	48	3	156/116	126/92	M	++	0	Calculus and infection	0	
37	M. O'B.	F	20	6	182/100	132/60	F (M)+	+++	+	Sl. right hydronephrosis, obesity, irregular menses	+	

TABLE 2.—MILD ARTERIAL HYPERTENSION WITHOUT RENAL DISEASE.

Case No.	Name.	Sex.	Age at onset and duration of hypertension (yrs.).		Extremes of blood pressure. Highest (mm. Hg).	Lowest (mm. Hg).	Constitutional components. Family history.*	Emotional instability.†	Physical signs.‡	Morphologic component.	Albumin in urine.§	Onset with:
38	S. K.	F	22	2	158/86	124/70	(M)++	++++	++++	Emotional tension	0	Marriage.
39	B. P.	F	19	5	148/92	122/80	F	++	++	Emotional tension, worry	±	Brother's death (hypertension).
40	L. S.	F	41	8	160/100	140/82	(M)+	++++	++++	Psychoneurosis, anxiety	0	Economic reverses.
41	S. D.	F	28	11	168/100	112/80	(M)+++	+++	++++	Psychoneurosis, anxiety	0	Pregnancy.
42	H. F.	M	20	1	170/100	140/82	M+ (F)++	+++	++	Not found	0	
43	J. F.	M	42	1	180/110	135/88	?	++++	+	Neurosyphilis ? psychoneurosis	±	
44	C. R.	M	28	3	190/115	125/95	(F)	++++	0	Hysteria; anxiety state	0	Marital maladjustment.
45	H. R.	M	27	5	190/110	140/90	0	+++	+++	Psychoneurosis ?	0	Marital maladjustment.
46	F. B.	M	17	1	160/90	120/70	?	++++	++	Emotional tension	0	Adverse home environ.
47	J. E.	M	17	1	162/110	118/70	?	+++	+++	Not found	0	
48	S. F.	M	23	8	180/100	144/88	F	++++	+++	Emotional tension, worry	0	Econ. maladjustment.
49	H. M.	M	28	12	180/110	134/86	—	+++	+	Psychoneurosis	0	
50	H. R.	F	41	4	186/114	146/90	M	++++	++++	Anxiety state; brain tumor	±	Econ. maladjustment.

* Family history: M = mother is hypertensive.
F = father is hypertensive.
(M) = hypertension present in family of mother.
(F) = hypertension present in family of father.
\+ = preceded by M or F = each member of mother's or father's family with hypertension.
S = hypertension present in a sibling.
0 = none; — = unknown; ? = possible but uncertain.

† Emotional instability—graded + to ++++.

‡ Physical signs—"Diencephalic" blush, excessive perspiration, cold extremities, dermatographia are each represented by +

§ Albumin in urine—by heat and acetic acid test: ± = slightest possible trace, approx. 0.7 to 0.14 gm., protein per L.;
\+ = faint trace, approx. 0.15 to 0.3 gm., protein per L.

In 11 of the remaining 13 cases nervous dysfunction had developed without renal disease (Table 2). Psychoneuroses were present in 6 cases; emotional disturbances in 5. These existed in combination with elements of the constitutional factor. In 1 instance hypertension appeared to have been influenced by treatment of an anxiety state (Case 44).

Precipitating Factor. In 5 instances emotional crises coincided with the onset of hypertension (Case 31). In 2 the onset occurred during pregnancy. In 2 infection of the urinary tract was present as a precipitating event (Case 14). In the remainder either the exact date of onset was not known, or gradually increasing emotional tension developed from adverse environmental influences. It could usually be inferred that the causes of such adversities lay in the individuals and not in their environments.

Case Reports. CASE 1.—H. K., a 19-year-old student, first became aware of arterial hypertension when he was 16, his blood pressure having been normal at age 15. At 17 he complained of headache, dizziness, and slight nausea. His mother developed hypertension at 40, and his sister also exhibited slightly elevated blood pressure. He blushed markedly all his life, perspired excessively, but denied emotional upsets. He was conscientious about his work, and his grades in college were excellent. On examination a blotchy, well-demarcated blush was seen over his cheeks, back and shoulders. His hands and feet were cold, slightly swollen, and intensely cyanotic, with a purple color slowly fading to dead white after elevation for a few minutes. His urine was not abnormal, and the function of his kidneys was not disturbed. Pyelograms taken after intravenous injection showed bilateral hydronephrosis, more marked on the right side. From the appearance of the films the presence of a horseshoe kidney was suspected. There was no infection. The blood pressure varied between 160 and 128 mm. Hg systolic and between 110 and 78 diastolic during 3 years of observation.

Summary (Case 1). Bilateral ureteral obstruction accompanied slight arterial hypertension in a young man with acrocyanosis and some of the components of the blushing syndrome.

CASE 10.—J. P. was 17 years old when slight hypertension was discovered on routine examination. His mother's systolic blood pressure was 184 and her diastolic 122 mm. Hg; 1 of her sisters suffers from a diseased kidney. At 17 his systolic blood pressure was over 140 mm. Hg, but on a subsequent examination it was normal. He was accepted as a recruit in the Navy. His mother refused to allow him to enlist because of his age, but the next year he applied for the Marines. His systolic pressure was found to be 160.

Physical examination disclosed nothing remarkable. There was marked dermatographia, his extremities were cold and moist, and a diffuse blush appeared on his face and chest after excitement. He was a tense, overactive, excitable, unstable individual, angering easily, becoming easily aroused, and relaxing with difficulty. There were no albumin or white blood cells in his urine, and on culture no organisms were grown. Pyelograms made after intravenous injection showed slight dilatation of the left renal pelvis. Angulation of the ureter was detected at the uretero-pelvic junction; on the right side there was an obvious abnormality which on retrograde

pyelography was found to be marked hydronephrosis with obstruction at the uretero-pelvic junction. In 30 minutes the right kidney excreted 13% of phenol red injected intravenously, the left 21%. His blood pressure varied from 164 to 144 mm. systolic and 94 to 60 mm. Hg diastolic. His two kidneys were able to concentrate urine to a specific gravity of only 1.016, but the clearance of urea was normal. Plastic repair (nephropexy) of the right kidney was performed by Dr. G. W. Fish in March, 1939; a large aberrant artery was found crossing the uretero-pelvic junction causing the constriction. Two months later his blood pressure was within normal limits, his kidneys were able to concentrate urine to a specific gravity of 1.025, and pyelograms showed that there was less obstruction on the right side. Six months after operation his blood pressure was normal, where it has remained, and he was accepted for enlistment in the Army.

Summary (Case 10). Arterial hypertension developed in a young man with marked hydronephrosis, and an unstable psychologic disposition. There was hypertension in the family. Relief of the obstruction by operation resulted in a return of the blood pressure to normal. The subsequent course is naturally in doubt.

CASE 12.—L. W. was an 18-year-old student. Both his father and mother suffer from arterial hypertension, the former also of some disease of his kidneys. Aside from otitis media at 3 his past was unimportant. He had always blushed with excitement, but denied emotional instability. He perspired excessively. His blood pressure was first found elevated on routine examination at the age of 14. He had complained of mild but frequent headaches and difficulty in concentration on his studies since the age of 17.

There was little of importance to be made out on physical examination. He was moderately obese. The function of his kidneys was normal. His heart was not enlarged in Roentgen ray photographs, and there were no abnormalities in the electrocardiogram. There was minimal albuminuria, but in the sediment were white blood cells, singly and in clumps. Cultures of the urine showed many colonies of streptococcus, Group D (Lancefield). Pyelograms taken after intravenous injection demonstrated slight but definite dilatation of ureters and renal pelves, and the calyces were somewhat blunted. His systolic pressure varied from 170 to 135 mm. Hg and his diastolic from 98 to 60 during 2 months' daily observation. He was given calcium mandelate by mouth for 2 weeks, and the number of organisms in each cubic centimeter of urine gradually decreased until the urine became sterile. One month later the same organisms were again obtained in cultures of the urine, again disappearing after the administration of calcium mandelate. This sequence of events had continued. Therapy had no effect upon the level of his blood pressure which remained slightly elevated.

Summary (Case 12). Arterial hypertension of mild degree lasted 4 years. The urine was infected, and lesions were observed in both kidneys. Treatment of the urinary infection did not affect the blood pressure.

CASE 14.—H. M. was a 17-year-old student. His father died of hypertension and uremia associated with one markedly contracted kidney; his paternal grandmother and 2 paternal uncles exhibit it. His appendix had been removed at the age of 15. Because of his family history, he had been observed since the age of 12, at which time his systolic pressure was 106 and his diastolic 54 mm. Hg. "Cold pressor test" gave a normal response, his systolic pressure rising 12 mm. Hg and his diastolic 6. At 13 his systolic

pressure was 130 and his diastolic 70; at 14, 122 and 78; at 15, 136 and 60 mm. Hg. When he was 16 he complained of lack of energy, fatigue, and slight dysuria, and he noticed emotional instability and irritability. Because his systolic pressure was 160 and his diastolic 80 mm. Hg he was studied in the hospital.

Aside from the presence of cold, moist extremities and dermatographia physical examination showed nothing remarkable. There was no albumin in the urine but microscopic examination disclosed the presence of many white blood cells singly and in clumps. Culture of the urine showed innumerable colonies of non-hemolytic streptococcus Group D (Lancefield). Pyelograms made after intravenous injection of diodrast demonstrated slight dilatation of the upper two-thirds of the right ureter, and blunting of the upper calyx of the right kidney; these findings were confirmed by retrograde pyelography which failed to disclose a cause for the dilatation. White blood counts and erythrocyte sedimentation rates were within normal limits, and there was no fever.

For a month in the hospital his systolic pressure varied from 170 to 118 and his diastolic from 94 to 50 mm. Hg. Therapy with sulfanilamide, urotropin, and calcium mandelate failed to eradicate the infection, but resulted in lowering the number of colonies of bacteria in the urine to 14 per cubic centimeter. When therapy was stopped, the number of colonies increased markedly. During the following year his blood pressure fell to normal levels when the infection was partially controlled, rising when the bacterial count in his urine was high. One year later he suffered two attacks of pyuria, with pain, nausea, and dysuria; his blood pressure again became further elevated during the acute episode. The same organism was found in his urine. The right ureter was therefore dilated by Dr. John Robinson in March, 1940; since then he has remained free of infection and his blood pressure has been normal.

The patient was a rather tense, shy individual, emotionally unstable but extremely active in school. He was well liked by his classmates, and attained a position of importance in the direction of their activities. He had always blushed easily when emotionally aroused, worried too much about his responsibilities and often became depressed. He perspired excessively, and his hands and feet were continually cold and moist. His tendon reflexes were hyperactive.

Summary (CASE 14). Arterial hypertension of slight degree became manifest coincidentally with infection of the urinary tract in a boy of 16, and was eventually controlled by relief of ureteral obstruction. There was hypertension in his family. He demonstrated signs of emotional and autonomic instability.

CASE 24.—M. W. was a 42-year-old physician, who first exhibited elevated blood pressure at the age of 32. His mother and one sister have slight hypertension. Between the ages of 23 and 38 he suffered 6 attacks of renal colic; 2 small calculi were passed. His blood pressure varied from 170 to to 144 mm. Hg systolic and 110 to 92 diastolic during 4 years' observation. He was an overconscientious and serious-minded individual, but did not worry to excess in spite of having many reasons for so doing. He did not consider himself emotionally unstable, and controlled himself well.

Important findings on examination were confined to the kidneys. There was bilateral hydronephrosis, greater on the right, and a small calculus was seen in the lower calyx of each kidney. There was obstruction at the right uretero-pelvic junction. There was no flush to be seen, and perspiration was not excessive. No essential change in his condition has occurred.

Summary (Case 24). Arterial hypertension was associated with relatively severe anatomic changes in the kidneys in a man with very little nervous instability.

CASE 26.—D. R. was 30 years old when her blood pressure was first elevated. Her mother died of hypertension and apoplexy. At the age of 26 she was told that she was suffering from a venereal disease, and she was treated weekly by injection for 2 years. This fact caused her great worry, and she began to brood. Her blood pressure was said to have been normal at age 28, but at 30 her systolic pressure varied from 174 to 144 and her diastolic from 106 to 84 mm. Hg. She admitted continuous worry, severe emotional instability, frequent crying spells, and nervousness.

On examination there was a well-marked blotchy blush on the face, neck and chest during excitement. The finger nails were bitten. Marked dermatographia was seen and perspiration was excessive. There were no other abnormalities. The urine was normal, as was the function of the kidneys. The heart was not enlarged in Roentgen ray photographs, and the electrocardiogram was not remarkable. Pyelograms after intravenous injection showed that there was constriction of both uretero-pelvic junctions, the insertion of the ureters being in the upper half of the renal pelves. The right kidney was ptosed. Her systolic pressure varied from 164 to 140 and her diastolic from 100 to 84 mm. Hg during 4 years. No evidence of syphilis was found by examination of the blood and spinal fluid.

Summary (Case 26). Labile arterial hypertension accompanied the hypertensive diencephalic syndrome and slight abnormality of the kidneys. There was in addition prolonged emotional tension.

CASE 31.—G. W. was an emotionally unstable, worrying woman of 37. Her mother suffered from arterial hypertension. She had always blushed easily, perspired excessively, and complained of coldness of the extremities. She had also noticed spontaneous bruises on her legs. Her first pregnancy occurred at the age of 35; a normal infant was delivered. Her second pregnancy occurred the following year; her blood pressure and urine were normal until the first week of the seventh month. At this time her child was seized by convulsions, later discovered to have been associated with teething. She became greatly excited and disturbed but remained calm to all outward appearances. During the next 2 days she felt tired and elated. Her ankles then became swollen, and her physician found marked albuminuria and arterial hypertension. Because of increasing signs of toxemia of pregnancy labor was induced in the middle of the seventh month, and twins were delivered. Her blood pressure remained slightly elevated after delivery

On examination 3 and 6 months later, there was a vivid but diffuse blush seen on the face and neck during excitement, and the extremities were cold and moist. The lower pole of the right kidney was palpable. The clearance of urea was 103% of normal and the kidneys were able to concentrate urine to a specific gravity of 1.039. There was a moderate amount of albumin in the urine, but no formed elements were found in the sediment, and cultures were sterile. The heart was not enlarged in Roentgen ray photographs. Basal metabolic rate was −14% of normal. Pyelograms after intravenous injection showed that very little diodrast was excreted by the left kidney and that the pelvis of the right was distorted; retrograde pyelography disclosed the presence of right hydronephrosis; there was distortion of the calyces on the left side. In 30 minutes the right kidney was able to excrete 8.6% of the phenol red injected intravenously, and the clearance of urea in this period was 50% of normal; phenol red excreted by the left kid-

ney was 4.1% and the clearance of urea was 35%. Her blood pressure varied from 162 to 142 mm. Hg systolic and 100 to 80 diastolic. It was slightly higher during the following 2 years.

Summary (Case 31). Arterial hypertension became manifest coincidentally with a severe emotional shock sustained during pregnancy. "Toxemia" resulted. Right hydronephrosis and diminished function of the left kidney were found 3 and 6 months later. The presence of infection was not established.

CASE 44.—C. R. was a 28-year-old clerk. Although his paternal grandfather died of apoplexy, there was no definite history of hypertension in his family. His blood pressure was said to have been normal until the age of 28, when his systolic pressure was 140 mm. Hg and his diastolic 90; 1 month later it had risen to 170 systolic and 100 diastolic, and 6 months later to 190 and 115. He did not complain of symptoms.

On examination there was nothing of importance to be made out. Renal function was normal and there were no abnormalities in the urine. The heart was not enlarged in Roentgen ray photographs; the basal metabolic rate was −9% of normal. He appeared to be a quiet, well-controlled, rather stolid and unemotional individual, denying all nervous manifestations. One week after discharge from the hospital he exhibited a typical attack of hysteria associated with an uncontrollable tic of his shoulders and arms which he admitted had been present before. Three months later he was found to be in a state of extreme nervousness, complaining of severe frontal headache and 6 months later these symptoms were unimproved. His systolic pressure varied from 190 to 150 mm. Hg and his diastolic from 120 to 88. He was sent to a psychiatric clinic for investigation; there he was considered to be suffering from psychoneurosis (anxiety state). Treatment was instituted, and subsequently his systolic pressure returned to normal levels, although his diastolic remained between 100 and 85 mm. Hg for 3 years.

Summary (Case 44). Arterial hypertension was associated with psychoneurosis, improving after psychotherapy.

CASE 45.—H. R. was a 30-year-old designer. His blood pressure first became elevated at the age of 27. His maternal grandmother died of hypertension. Except for otitis media and pneumonia his past history was uneventful. He had always been emotionally unstable, but usually remained outwardly calm during periods of intense internal excitement. Perspiration was profuse. He had suffered from frequent occipital headaches for many years, usually brought on by excitement.

Little of importance was made out on examination. A faint blotchy blush was seen over the face and chest, and the extremities were cool and moist. Renal function was normal, and there were no abnormalities in the urine. Basal metabolic rate was −5%. The heart was not enlarged in Roentgen ray photographs, and his electrocardiogram was not unusual. Pyelograms after intravenous injection disclosed normal pelves and ureters. No bacteria were found on culture of the urine. His systolic pressure was variable, with a range of 190 to 140 mm. Hg; his diastolic varied likewise from 120 to 90.

During 2 years' observation it became obvious that he was extremely high strung and nervous. Sometimes he acted in an erratic fashion, and there were many marital and environmental adjustments which he could

not make. He worked at several different trades, did well in all, but refused to remain at a job long enough to secure financial stability for his family. He finally left his wife, and went to another part of the country.

Summary (Case 45). Arterial hypertension was associated with emotional instability in a maladjusted young man of some ability.

Discussion. The cases reported probably represent instances of the earliest stage of arterial hypertension. Every one exhibited at some time elevation of both systolic and diastolic pressures to a degree greater than the limits set by Hines.[3] His and other studies[1,5] indicate that similar individuals often develop persistent arterial hypertension later in life. That renal disease was present in so many of them (74%) is further evidence of the part the kidneys play in arterial hypertension. Diseases of the kidneys occurred too commonly to be explained as coincidences; it is likely therefore that they are concerned with at least part of the cause of elevation of the blood pressure.[6b] The absence of renal diseases in the remainder suggests that they were present but not demonstrable, or that arterial hypertension is the result of more than one condition. The latter explanation is more likely.

From these and other studies it is possible to draw several tentative conclusions. It is obvious that arterial hypertension is not a single condition resulting from a single cause, but is the result of several factors, one or more of which is dominant. There is little doubt, for example, that organic renal disease and hypertension are intimately associated. That fact emerges when the state of the kidneys is examined;[6b] but renal disease often exists when the blood pressure is normal. Contrariwise, arterial hypertension may occur without renal disease. Other factors need furthermore to be taken into account, such as the hereditary nature of hypertension[2] and the tendency to "nervousness" in hypertensive individuals, for many years considered important.

An attempt has been made here to separate those aspects that can be studied from those that cannot. The view taken is that one or more abnormal states is by chance found to affect individuals constitutionally predisposed. Most of the signs of this predisposition can be referred to the nervous system. When an individual exhibits these signs, and subsequently develops renal disease, abnormal emotional reactions to his environment, or one of several other conditions, he becomes subject to hypertension. This conception does not help to explain the precise mechanism, but it does propose a direction for making explorations. The fundamental defect, that of individual susceptibility—the "constitutional component"—remains "essential," or unknown (agnogenic).

In the light of this study it is possible to ascertain some of the *effects* of hypertension usually regarded as being present in the more advanced stages of the disease as its necessary accompaniments.

For example, elevation of the blood pressure itself either contributes to the usual state of "nervousness" often seen in hypertensive individuals, or nervousness is antecedent to that elevation. In the present series now reported increased nervous tension was known to be present in most of the patients before hypertension was discovered, and was associated with very little elevation of blood pressure after its discovery. This observation suggests that "nervousness" is concerned in the cause of hypertension.

This study has been illuminating in that it has been possible to observe in a group of individuals believed to represent the early stages of a chronic disease, arterial hypertension, certain pathologic and functional derangements with which later stages are associated. These derangements may therefore play a part in causation.

Summary. Fifty patients exhibiting slight elevation of the blood pressure were studied with a view to ascertaining the varieties of clinical disturbance. Thirty-seven were found to be suffering from various diseases of the kidneys, and 11 others from dysfunctions of the nervous system. In addition, every patient exhibited nervous tension of some degree. In a few cases the onset of hypertension was associated with a definite physical or psychologic disturbance. It is probable in the light of this experience that arterial hypertension is the result of a number of factors, differing in different individuals.

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EXPERIMENTAL CHRONIC HYPERTENSION IN THE RAT.*

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Our generally accepted notions concerning the etiology and nature of chronic hypertension are based for the most part on experiments performed on the dog and on clinical observations on human patients. With the development of a relatively simple and

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accurate method for the determination of the blood pressure of the rat (*Mus norvegicus*), it is possible to utilize the advantages which the use of this species offers to investigate many problems not easily solved when the larger mammals or the human are the subjects of study. A variety of procedures lead to the development of chronic hypertension in the rat and may be used conveniently in the investigation of various problems of experimental hypertension.

The Determination of the Systolic Blood Pressure. Systolic blood pressures were determined on unanesthetized adult rats by the method previously described.[8]

This procedure has proved accurate and reliable in our hands. Several precautions, however, may be emphasized which must be taken into account to avoid errors. The rubber sleeve in the plethysmograph must be neither too taut nor loose; otherwise the water manometer will not respond to alterations of bloodflow in the tail. By avoidance of undue tension or slack in the rubber, maximum sensitivity is obtained and only minimal warming of the animal is necessary to give a good reading. Overheating of the animals is to be avoided.

The same criteria are to be applied to the reading of the movement of water in the manometer connected to the plethysmograph as are used in graphic methods for determining the blood pressure in man. The response of the plethysmograph must be sharp and the movement of the column of water should continue when the mercury column is maintained at a point 5 to 10 mm. below the level at which the water column begins to move.

If these precautions be observed and if overheating of the animals be avoided, accurate values are readily obtained and there is little chance of deception by too low values due to inadequate dilatation of the arteries in the tail or too high values induced by overheating.

Effects of Various Procedures on Blood Pressure. Most of the rats used were of a piebald strain reared in the laboratory. Some of a pure-bred Wistar strain were obtained from a commercial breeder.

Hypertension has been induced by the following methods: 1, by the procedure of partial nephrectomy; 2, by the application of silk to the renal cortex; 3, by the application of a collodion capsule to the kidney; 4, by the injection of a suspension of kaolin into the cisterna magna; 5, by the administration of excessive doses of certain steroidal compounds; and 6, by the administration of various nephrotoxic agents. In addition to the increased blood pressure following the above procedures, hypertension has been observed to occur in certain other rats. In some of these the presence of spontaneous hydronephrosis probably accounts for the existing hypertension. Other animals had been subjected to various experimental diets and these observations will be described in a later communication.

1. *Partial Nephrectomy.* The procedure of partial nephrectomy consists in ligating the poles of one kidney and removing the other, as described by Chanutin and Ferris.[1] This procedure suffers from the defect that it requires accurate estimation of the amount of renal tissue to be removed. If too much be extirpated, the animal succumbs within a few weeks, due to the development of renal insufficiency or malignant hypertension or both. On the other hand, if too little tissue be removed, no appreciable elevation of the blood pressure results.

The renal stump remaining after partial nephrectomy is frequently closely adherent to the surrounding viscera (liver, spleen) and large blood-vessels may be seen to be growing into the renal substance from its adherent tissues. This is particularly apt to occur if one amputates the poles of the kidney by cutting rather than by ligation, as recommended by Chanutin and Ferris. To avoid the formation of this collateral blood supply which may prevent the development of hypertension we have adopted the procedure of cauterizing the cut surface of the kidney.

Although used exclusively for our earlier studies, the method of partial nephrectomy has proved much less satisfactory than the application of silk to be described next. Attempts to induce hypertension by scarring the surface of the kidney, by the cautery, or by the application of escharotics (silver nitrate, tincture of iodine, phenol) proved futile. Mere destruction of the renal cortex is unsatisfactory, since it either fails to induce hypertension or results in so much renal destruction as to induce a rapidly fatal renal insufficiency.

2. *The Application of Silk.* For the induction of chronic hypertension experimentally we have found the application of silk to be the procedure of choice. This method was first described for the dog by Page.[6] In applying it to the rat, the following method is used.

A piece of silk* (the cloth commercially designated as "crepe" silk is best) is cut into oval shape. Four V-shaped pieces are cut out at each quadrant and a purse-string suture is passed around the edges (Fig. 1). The kidney is exteriorized through a lumbar incision, the capsule broken and pushed aside by gentle pressure with a gauze sponge and the silk applied (Fig. 1). The suture is drawn together and tied. Care must be taken to avoid obstruction of the ureter or renal pedicle. It is only necessary to apply the silk lightly. The application of the ligature just below the poles prevents the silk from slipping off when the kidney is replaced in the abdomen.

Except in rare instances where a rat has a spontaneous slightly elevated blood pressure prior to the procedure described above, it is necessary to apply silk to the other kidney in order to obtain permanent elevation of the blood pressure. This is done about 1 week

* Cotton cloth is equally satisfactory and has been substituted for the silk in all our recent experiments.

following the first operation. Extirpation of the second kidney results, in many animals, in a rapidly developing malignant hypertension and death within a few weeks following nephrectomy. Where the more chronic type of hypertension is desired, the bilateral operation, as just described, is necessary.

The above described procedure has proved satisfactory in our hands. The use of cellophane instead of silk, as originally advocated by Page[6] in the dog, is rather cumbersome when applied to the rat and in our experience is unsatisfactory, due to the development of a "foreign-body" reaction with erosion of contiguous organs. The immediate mortality of the operation when using silk is low and if care be taken to avoid compression of the pedicle, the animal develops hypertension gradually and remains in good health for some months.

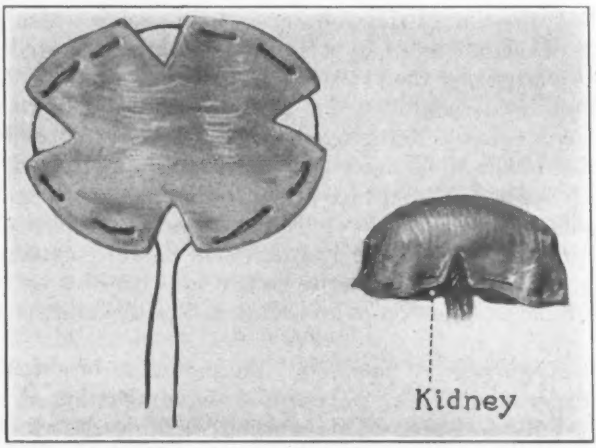

FIG. 1.—Application of silk to the kidney. The drawing on the left illustrates the manner in which the silk is prepared with a purse-string silk suture. On the right is shown the appearance of the kidney with the silk applied. Note that the renal hilus is not compressed by the procedure.

A distinct rise in blood pressure following the application of silk bilaterally may be evident within 10 days following the second operation, but usually does not occur until several weeks have elapsed.

A typical result following the application of silk is illustrated in Chart 1, which depicts the blood pressure curve of a single rat observed for more than 4 months. Except for the irregularity during the third week following the application of silk to the second kidney, the curve shows a uniform and gradual rise until just a few days before the death of the animal, when there is a precipitous premortem drop. By the time the systolic pressure attains a level of 200 mm., there is evidence of renal insufficiency, the animal develops

uremia, becomes anemic, loses weight and manifests a general state of debility in which it succumbs.

The age of the animal is an important factor in determining the reaction of the rat to the application of silk to the kidneys, as well as to the procedures to be described next. Young animals, even after reaching maturity, react poorly and tend to develop uremia and malignant hypertension. Older animals (over 1 year of age) withstand the operations better and tend to develop a chronic form of hypertension.

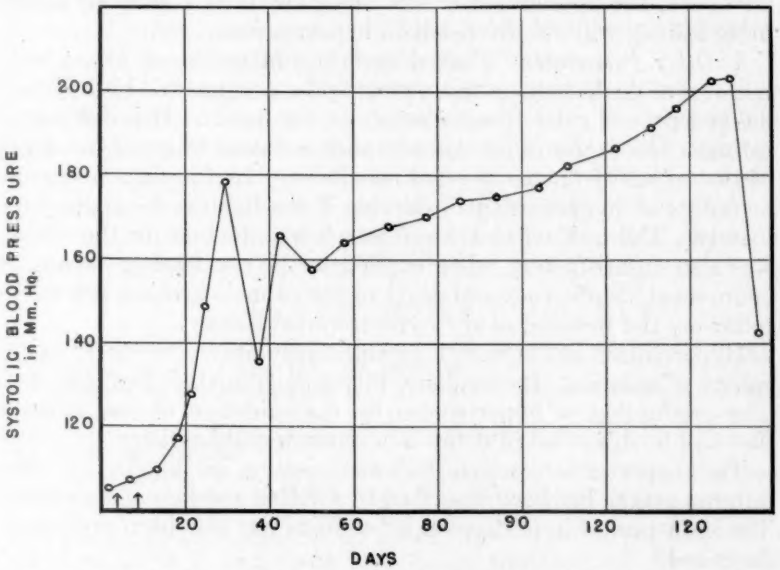

CHART 1.—Variations in the systolic blood pressure of a rat following the application of silk bilaterally. The arrows indicate the application of the silk with an interval of 5 days between the operations on the two kidneys. Note the temporary elevation which occurred about 3 weeks following the operation with the subsequent remission. After 6 weeks the blood pressure curve remains at a hypertensive level, rising gradually over a period of 5 months when it drops precipitously before the death of the animal.

3. *The Application of a Collodion Capsule.* Another satisfactory procedure for inducing hypertension in rats consists in applying a coat of collodion to the renal cortex. This may be done by covering the decapsulated kidney with a single layer of ordinary surgical gauze and applying collodion.* The kidney should remain exteriorized for several minutes until the solvent evaporates from the solution of collodion, leaving a white firm coat on the kidney.

A collodion capsule may also be applied using silk, as described in the preceding section. For this purpose silk of the type used in

* The use of collodion was suggested to us in a conversation with Dr. W. Dock. (See also Page, E. W., Patton, H. S., and Ogden, E.: Am. J. Obst. and Gynec., **41**, 53, 1941.)

the manufacture of women's stockings is desirable. The collodion is applied after the silk has been tied over the kidney in the usual manner.

The application of collodion to the kidney results in more extensive injury to the organ than when silk alone is applied. Removal of the second kidney is usually followed by a rapid elevation in blood pressure and death of the animals in a short time. A number of animals develop hypertension following a unilateral operation. In those which fail to develop hypertension in the course of 6 to 10 weeks, the application of silk alone (without collodion) to the other kidney will usually result in hypertension.

4. *Other Procedures.* Partial occlusion of one renal artery with removal of the kidney on the opposite side, as suggested by Rytand,[7] has not proved entirely satisfactory in our hands. It is difficult to estimate the degree of occlusion in such a way as to avoid the death of the animals from acute renal insufficiency by too tight a ligature or failure of hypertension to develop if the ligature be applied too loosely. The method of Drury,[2] which was devised for the rabbit, was also unsatisfactory when applied to the rat, leading usually to acute renal insufficiency and death of the animals within a few weeks following the removal of the hypertrophied kidney.

Hypertension has occurred spontaneously only very rarely in our colony of animals. Its incidence in young animals is less than 1%. The production of hypertension by manipulation of the animal's diet will be described in detail in a separate publication.

The hypertension which follows injection of kaolin into the cisterna magna has been described by Griffith and his collaborators.[3] The induction of hypertension by steroids has also been previously described.[4]

In view of the variety of substances which are available for producing renal damage, it was thought that some of these might incidentally also induce hypertension. This procedure has, in general, not proved satisfactory in our hands. We have administered a number of agents which induce renal injury (bichloride of mercury, uranium nitrate, cantharides, lead nitrate, various sulfonamide derivatives, and so on) in doses which were fatal to only 10% to 20% of the animals. In only approximately 10% of all animals in which marked renal damage had been produced did a moderate degree of hypertension develop. This result is compatible with the view that renal damage alone does not result in hypertension but that a specific portion of the nephron must be affected before hypertension develops. This point of view will be dealt with more fully in a separate communication.

Discussion. The procedures outlined afford a means of inducing hypertension by what appears superficially to be a variety of unrelated agencies. There would thus appear, offhand, to be little connection between the hypertension resulting from injecting kaolin

into the cisterna, the feeding of sterols, and the application of silk to the kidney. Nevertheless, as discussed elsewhere,[5] there is evidence which suggests that all of these procedures may act directly or indirectly through the kidney and thus give rise to hypertension of renal origin.

For practical purposes the bilateral application of silk is, in our experience, the optimal method for inducing chronic hypertension. By this procedure, mortality is slight and the resulting hypertension is of long duration. With more intensive procedures, the hypertension resembles that of malignant hypertension, as observed in man, the blood pressure rising to very high levels in a period of several weeks and the animal rapidly succumbing in uremia.

Summary. A variety of procedures are outlined by which it is possible to induce chronic hypertension in the rat. The most practical of these procedures consists in applying silk to the kidneys. This is accompanied by relatively low operative mortality and usually results in a permanent elevation of pressure to hypertensive levels. The blood pressure responses to various other operative procedures on the kidneys are described.

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SERUM CHOLESTEROL AND ATHEROSCLEROSIS IN CHRONIC GLOMERULONEPHRITIS.

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The observation that atherosclerosis occurs commonly in individuals dying of renal disease is generally accepted. Ophüls[5a] reported that in a group of 155 autopsies of cases of chronic lesions in

the kidney, 93% had definite and frequently marked atherosclerosis. Likewise, more recent studies by Fishberg[4] and by Addis and Oliver[1] report a similar incidence. One of the postulated factors as an explanation for the almost constant coëxistence of the two processes is the elevation in serum cholesterol which may occur during some stage of the renal disease.[3,6] In view of the great frequency of atherosclerosis in individuals over the age of 40 years, it was felt desirable to determine first the incidence of atherosclerosis in young persons dying of renal disease and, second, the frequency and the extent of elevation of the serum cholesterol in such patients.

Material. Two groups of patients were studied. In the first, the clinical records and autopsy protocols of 54 patients under the age of 40, who had died of subacute or chronic glomerulonephritis at the Presbyterian and Babies' Hospital during the past 10 years, were examined. The incidence of these two types of renal disease in this group was as follows: chronic glomerulonephritis in 47 instances, subacute glomerulonephritis in 7. The available serum cholesterol values were tabulated. The degree and extent of gross aortic and coronary atherosclerosis as noted by the pathologists was recorded and subdivided into three classes: mild, moderate, and marked. Mild atherosclerosis was considered to be present if several small, raised, yellow plaques were visible in either the aorta or coronary arteries. Marked atherosclerosis was designated to include widespread, numerous lesions. Moderate atherosclerosis was considered to fall between these two extremes.

In the second group, the case records of 18 patients with chronic glomerulonephritis who were being closely observed at the Research Service, First Division, Welfare Hospital over periods up to 2 years were examined and the serum cholesterol determinations tabulated. In this study all of the cholesterol determinations were done on serum by the method of Bloor, Pelkan, and Allen[2] except 8 patients in Group I under the age of 10 years in whom the method of Schoenheimer and Sperry[7] was used. In the first group, cholesterol determinations had not been done frequently and values were available in only 30 of the 54 cases.

In the second group of patients cholesterol determinations were made at approximately monthly intervals. The number of recorded values in each of the patients varied from 4 to 23, averaging 8 for the group.

Occurrence of Gross Atherosclerosis. An analysis of the pathology protocols of the 54 patients in the first group, individuals age 1 through 39 dying of renal disease, revealed that gross atherosclerosis of the aorta occurred in 52 instances, or in 96% of the group. Coronary atherosclerosis was recorded in 38 instances, or in 70% of the group. Coronary atherosclerosis was not present in the absence of at least mild aortic lesions. Table 1 reveals the incidence and extent of gross aortic and coronary atherosclerosis in the patients of this group who were subclassified according to age into the four decades. It is of interest that gross mild to moderate aortic atherosclerosis was present in 7 of the 8 individuals in the age group 1 to 9 years. No coronary lesions were observed in this group. However, in the next three decades, coronary atherosclerosis was

almost as prevalent as aortic atherosclerosis. The lesions were more widespread and frequently of greater magnitude in the third and fourth decades (see Table 1).

TABLE 1.—OCCURRENCE OF GROSS AORTIC AND CORONARY ATHEROSCLEROSIS IN GROUP I (54 PATIENTS, AGE 1 TO 39, DYING OF CHRONIC GLOMERULONEPHRITIS).

Age groups (in years):	0–9.	10–19.	20–29.	30–39.	Total.	%.
Number of patients	8	7	18	21	54	
Aortic atherosclerosis	7	6	18	21	52	96
Mild	4	3	3	5	16	
Moderate	3	3	12	12	31	
Marked	0	0	3	4	7	
Coronary atherosclerosis	0	5	16	17	38	70
Mild	0	3	7	7	17	
Moderate	0	2	8	8	18	
Marked	0	0	1	2	3	

The prevalence of atherosclerosis of the aorta and coronary artery in this group may be compared with the incidence of lesions in 54 patients in the same age groups selected at random from the autopsy records (Table 2).

TABLE 2.—OCCURRENCE OF GROSS AORTIC AND CORONARY ATHEROSCLEROSIS IN A CONTROL GROUP OF 54 PATIENTS COMPARABLE IN AGE TO GROUP I.

Age groups (in years):	0–9.	10–19.	20–29.	30–39.	Total.	%.
Number of patients	8	7	18	21	54	
Aortic atherosclerosis	0	1	6	12	19	35
Mild	0	1	5	8	14	
Moderate	0	0	1	4	5	
Marked	0	0	0	0	0	
Coronary atherosclerosis	0	1	2	8	11	19
Mild	0	1	2	6	9	
Moderate	0	0	0	2	2	
Marked	0	0	0	0	0	

The only persons excluded from this sampling were those dying of renal disease comparable to Group I. An analysis of the autopsy protocols of the control series revealed that gross aortic atherosclerosis was present in 19 individuals, or in 35% of the group. Gross coronary atherosclerosis was recorded in 11 instances, or in 19% of the 54 patients.

The difference between the two groups is more striking in the first two decades since atherosclerosis was present in 14 out of 15 instances in Group I, in contrast to only 1 of the 15 in the control group. In addition, the degree of lipoid infiltration, when present in this group, is less marked than in the Group I patients dying of renal disease (Table 2).

Serum Cholesterol Values in 54 Patients With Glomerulonephritis (Group I). Serum cholesterol determinations were recorded in 30 of the 54 patients in Group I. A total of 77 determinations had been made. In 11 of the individuals, 3 or more determinations were available. In 17 of the 30 patients, the serum cholesterol value

exceeded 300 mg. per 100 cc., in 11 the value exceeded 400 mg. per 100 cc., and in 7 the value exceeded 600 mg. per 100 cc. The following abstract is characteristic of the cases that were followed over long periods of time.

CASE 1.—E. D., a white schoolgirl, aged 11½ years, entered the Babies' Hospital on July 16, 1937, with the history of pallor and generalized edema of 4½ months' duration. In the past history, the patient had had tonsils and adenoids removed at the age of 2½, and scarlet fever at the age of 8 years. Subsequent urine examinations were negative. Onset of the present illness was preceded by an upper respiratory infection, *i. e.*, "stuffy nose" and sore throat. Swelling of eyelids first appeared and then became generalized. Urine examination showed albumin, red blood cells, white blood cells, and casts. Edema gradually became worse in spite of fluid restriction and the patient was admitted to the hospital.

On physical examination, the patient was very pale and had generalized anasarca. She was alert, coöperative, and not uncomfortable. The temperature was 99.8° F., the pulse rate 90, respiratory rate 20, and the blood pressure 160/110. There was a moderate thickening of both mid-turbinates with a mucopurulent discharge. In the fundi the arteries were constricted and the nerve head slightly elevated. The lungs were clear. The heart was normal. In the abdomen, shifting dullness was present. No masses or organs were felt. There was no lymphadenopathy or abnormal neurologic findings.

Laboratory data on admission revealed red blood cells 3,350,000, hemglobin 11.9 gm. per 100 cc., white blood cells 13,000 with 69% neutrophils. The urine was straw-colored, cloudy, with a specific gravity 1.022, albumin 4+, and the urinary sediment contained red and white cells with granular and hyaline casts. The blood urea nitrogen was 10 mg. per 100 cc., the total serum proteins 3.35 gm. with albumin 1.52 and globulin 2.05 gm. per 100 cc. Six serum cholesterol determinations were recorded. On March 17 the serum cholesterol was 689 mg., on April 3, 717 mg., on April 13, 724 mg., on May 3, 686 mg., on June 2, 611 mg., and on June 28, 280 mg. The patient was placed on a high protein diet, low in salt, with fluids restricted to 1000 cc. daily.

She felt fairly well with edema moderately well controlled by diuretics until June 24, when chills and fever developed with signs of peritonitis. Blood and abdominal fluid culture revealed pneumococcus Type XVIII. The patient gradually failed and died on June 29.

On postmortem examination the following diagnoses were made: 1, Chronic glomerular nephritis; 2, anasarca and ascites; 3, cardiac hypertrophy, mild; 4, septicemia; 5, peritonitis; 6, atheromata of aorta and coronary arteries. The gross lesions in the aorta and coronary arteries were elevated, yellow atheromatous patches. These were present in the anterior descending branch of the left coronary and in the right coronary artery as well as in the aorta. These lesions were especially numerous just above the sinuses of Valsalva.

Serum Cholesterol Values in 18 Patients With Chronic Glomerulonephritis Now Being Observed (Group II). The serum cholesterol values in the 18 patients with chronic glomerulonephritis (Group II) are compiled in Table 3. In each of the individuals, the total number and range of serum cholesterol determinations, together with the number of values above and below 400 mg. per 100 cc. are recorded. In 17 of the 18 individuals the high cholesterol value

exceeded 400 mg. per 100 cc., and in 10 of the 18 the high value exceeded 600 mg. In contrast, the low serum cholesterol value for each patient varied from 167 to 450 mg. per 100 cc. In 9 of the individuals the low value was less than 300 mg.

TABLE 3.—SERUM CHOLESTEROL VALUES IN 18 PATIENTS WITH CHRONIC GLOMERULONEPHRITIS (GROUP II).

Pt.	Age.	Sex.	No. of determinations.	No. of determinations over 400 mg. per 100 cc.	No. of determinations under 400 mg. per 100 cc.	Range of serum chol., mg./100 cc.	
						High.	Low.
A. L.	14	M	5	2	3	446	375
H. B.	24	F	19	10	9	537	292
S. R.	26	F	6	6	0	610	450
J. T.	25	M	6	3	3	1000	317
A. P.	17	F	12	0	12	339	167
E. B.	23	M	10	3	7	610	225
H. R.	25	M	5	3	2	458	384
A. A.	28	F	4	1	3	438	251
C. M.	41	M	4	3	1	450	355
A. H.	51	M	6	4	2	948	274
W. E.	17	M	5	3	2	807	305
P. B.	30	M	5	4	1	617	370
J. W.	21	F	5	2	3	400	300
D. G.	20	M	4	2	2	792	397
H. P.	17	F	23	2	21	417	250
D. L.	26	M	4	1	3	447	255
A. R.	36	M	13	7	6	730	310
E. T.	41	F	12	10	2	710	297
Total	..	..	143	77	66		

(Normal values, variously given, range about 140–300 mg. per 100 cc.)

It is evident from Table 3 that if only isolated determinations of serum cholesterol had been made, a number of instances of significant hypercholesterolemia would not have been observed, for in 66 of the 143 determinations the value obtained did not exceed 400 mg. per 100 cc. The period of hypercholesterolemia was associated in most instances with an edematous phase of glomerulonephritis. From clinical observation of these patients over long-term periods it was observed that when the edema subsided, the serum cholesterol values fell towards normal levels.

Discussion. Atherosclerosis has been found to occur in 96% of the individuals (age: 1 through 39 years) dying of renal disease in the group studied, in contrast to 35% in a control group with the same age distribution.[1] This difference between the groups is more striking when compared with the incidence of atherosclerosis obtained by Ophüls[5b] in a statistical survey of 3000 autopsies. This author reported only a few scattered cases during the first two decades, 3.5% during the third decade, and 9.2% during the fourth decade. The greater incidence of atherosclerosis in the control group as compared to this large series may be explained in part by the interpretation of the presence of atherosclerosis. If several raised, yellow, intimal lesions were present in either the aorta or

the coronary arteries, this was regarded as sufficient for a diagnosis of mild atherosclerosis.

It has also been shown in the above data that hypercholesterolemia almost invariably occurs in patients with chronic glomerulonephritis during some stage of the disease process—particularly in association with the nephrotic stage. Likewise there is considerable fluctuation in the serum cholesterol levels in these patients in contrast to normal individuals in whom the cholesterol level has been found to remain relatively constant over long periods of time.[8–10] The hypercholesterolemia, which occurs in other diseases, namely myxedema and poorly controlled diabetes, is likewise associated with a high incidence of atherosclerosis. It seems possible, therefore, that the elevation in serum cholesterol which occurs in renal disease is one of the factors responsible for the development of aortic and coronary atherosclerosis.

It has also been demonstrated that atherosclerosis has occurred with great frequency in a young age group, in which atherosclerosis ordinarily is relatively rare. For this reason, the etiologic significance of senescence which is so frequently considered paramount in the development of atherosclerosis can be depreciated, at least as far as the present study is concerned.

Conclusions. 1. Fifty-two of 54 patients (96%), aged from 1 through 39 years, dying of chronic glomerulonephritis, had gross aortic atherosclerosis. In 38 (70%) of these patients, gross coronary atherosclerosis was present.

2. Serum cholesterol values in 30 of these 54 patients exceeded 300 mg. per 100 cc. in 17. In 12 of these individuals the value exceeded 400 mg. per 100 cc.

3. Serum cholesterol studies have also been carried out in a group of 18 patients with chronic glomerulonephritis observed over periods up to 2 years. Hypercholesterolemia was present in all of the group on one or more occasions. In 17 of the 18 patients the cholesterol value exceeded 400 mg. per 100 cc. In 10 of these the value exceeded 600 mg. per 100 cc.

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INSTANCES OF DISAGREEMENT IN THE RESULTS OF TWO TYPES OF ORAL GLUCOSE TOLERANCE TESTS.

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In the course of performing 160 2-dose, 1-hour glucose tolerance tests (Exton-Rose[4a] procedure) it seemed that this test was more sensitive than the conventional 1-dose test. It is the purpose of this paper to present selected instances where the 1-dose, 2-hour and the 2-dose, 1-hour glucose tolerance tests were performed on the same individual in order to determine the relative merits of the two tests and evaluate proposed criteria for their interpretation.

A review of the literature reveals three papers dealing with a comparison of the 2-dose and the 1-dose tests.

Kelly, Beardwood, and Fowler[9] found the two tests to be in close agreement and cite only 2 cases out of 50 where disagreement occurred when both tests had been performed in the same individual. These authors place their reliance in the 2-dose, 1-hour test. Young[18] studied 4 individuals with presumably normal carbohydrate metabolism and found the 2-dose test to be abnormal in each instance whereas the conventional 1-dose test resulted normally. He felt that the 2-dose test was in error. Brown[1] reported the results of both tests performed in each of 24 subjects. He considered the two tests to be equally accurate.

Methods. Individuals were selected upon whom we had obtained borderline or slightly abnormal 2-dose tests, that is, a 1-hour blood sugar value of 160 mg. per 100 cc. or more by the analytical method of Folin and Malmros.[5] At the time of study none of the group was overweight, arteriosclerotic, or suffering from an infection. As far as could be determined, no other factor which might have influenced the glucose tolerance was operative. All of the individuals used in this study except Cases 13 and 14 are well known to us and have had other studies of their glucose metabolism made. Three individuals were known to have had glycosuria with a normal glucose tolerance for a number of years. All of the subjects studied were in good health and without past history or symptoms of diabetes except in Cases 6 and 16, who were suspected of having latent diabetes. Care was taken to provide for an adequate antecedent diet since it has been shown by Sweeney,[14] Conn[2] and others that antecedent diet markedly affects glucose tolerance, and by Sweeny, Muirhead and Allday[15] and Langner and Fies[10a] that a diet inadequate in carbohydrates influences the 2-dose test as well as other glucose tolerance tests.

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A review of the literature reveals three papers dealing with a comparison of the 2-dose and the 1-dose tests.

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Methods. Individuals were selected upon whom we had obtained borderline or slightly abnormal 2-dose tests, that is, a 1-hour blood sugar value of 160 mg. per 100 cc. or more by the analytical method of Folin and Malmros.[5] At the time of study none of the group was overweight, arteriosclerotic, or suffering from an infection. As far as could be determined, no other factor which might have influenced the glucose tolerance was operative. All of the individuals used in this study except Cases 13 and 14 are well known to us and have had other studies of their glucose metabolism made. Three individuals were known to have had glycosuria with a normal glucose tolerance for a number of years. All of the subjects studied were in good health and without past history or symptoms of diabetes except in Cases 6 and 16, who were suspected of having latent diabetes. Care was taken to provide for an adequate antecedent diet since it has been shown by Sweeney,[14] Conn[2] and others that antecedent diet markedly affects glucose tolerance, and by Sweeny, Muirhead and Allday[15] and Langner and Fies[10a] that a diet inadequate in carbohydrates influences the 2-dose test as well as other glucose tolerance tests.

These selected individuals were also subjected to the conventional 1-dose, 2-hour technique in which a single dose of either 50 or 100 gm. of glucose was administered (Table 1). Our criterion for a normal response to this test requires that the fasting blood sugar shall be less than 120 mg. per 100 cc., the ½-hour value shall be 180 or less, and the 2-hour value for venous blood sugar shall be 120 mg. per 100 cc. or less. These criteria are commonly used in insurance practice. Even if the critical 2-hour level is reduced to 110 mg. per 100 cc. it would not cause any difference in the interpretation of the results in Table 1. For a discussion of these criteria we refer the reader to McCrudden,[11] Joslin,[8] Exton and Rose,[4a] and Watson.[17]

Both types of glucose tolerance tests were performed in the morning after an overnight fast. In 10 of the cases we were able to obtain simultaneous samples of capillary blood from the finger and venous blood from the antecubital vein. In these cases duplicate determinations were performed on each sample of capillary and upon each sample of venous blood by the method of Folin and Malmros. The average of the duplicates in each instance is recorded in Table 1. In the other 6 subjects only capillary or only venous blood was obtainable as will be seen upon consulting Table 1.

Criteria for the Interpretation of the 2-Dose, 1-Hour Glucose Tolerance Test. According to the criteria of Exton and Rose,[4b] a normal response required: 1, a normal fasting blood sugar; 2, a rise which did not exceed 75 mg. per 100 cc. in the ½-hour specimen; and 3, a 1-hour blood sugar value which did not exceed the ½-hour value by more than 10 mg. per 100 cc. We feel that their criteria were too strict in limiting the allowable rise during the second ½-hour to 10 mg. per 100 cc.

Gould, Altshuler, and Mellen[7] showed that a 30 mg. per 100 cc. rise could occur during the second ½-hour in a normal individual. Their other requirements were a normal fasting blood sugar level and a rise during the first ½-hour not in excess of 50 mg. per 100 cc. These authors concluded that if at least two or the three requirements were fulfilled the individual could be considered as normal.

Cooperstock and Galloway[3] found that in normal children a total rise of 80 mg. per 100 cc. could occur in 1 hour when capillary blood was employed.

Matthews, Magath and Berkson[13] found that the 1-hour blood sugar value served as the most useful criterion and they did not depend upon the rise or fall pattern of the curve. Their critical level was established as 158 mg. per 100 cc. at the end of 1 hour when samples of venous blood were obtained and analyzed by the method of Folin and Wu. Below this level none of the individuals studied were diabetic. When the hour blood sugar level was between 160 and 180 mg. per 100 cc. the case was considered borderline since blood sugar values in 5.1% of normals and 7.7% of very mild diabetics studied by these authors fell into this range. When the 1-hour value was in excess of 180 mg. per 100 cc. all the individuals observed proved to be diabetic.

We accepted the critical 1-hour level of Matthews *et al.*[13] because it diagnosed all of our causes of diabetes correctly, whereas the

criteria of Gould *et al.*[7] failed to make the correct diagnosis of diabetes in 4 cases observed by us. The highest 1-hour value in our series obtained in the case of a presumably normal individual was 192 mg. per 100 cc.

TABLE 1.—COMPARISON OF BORDERLINE GLUCOSE TOLERANCE TESTS.

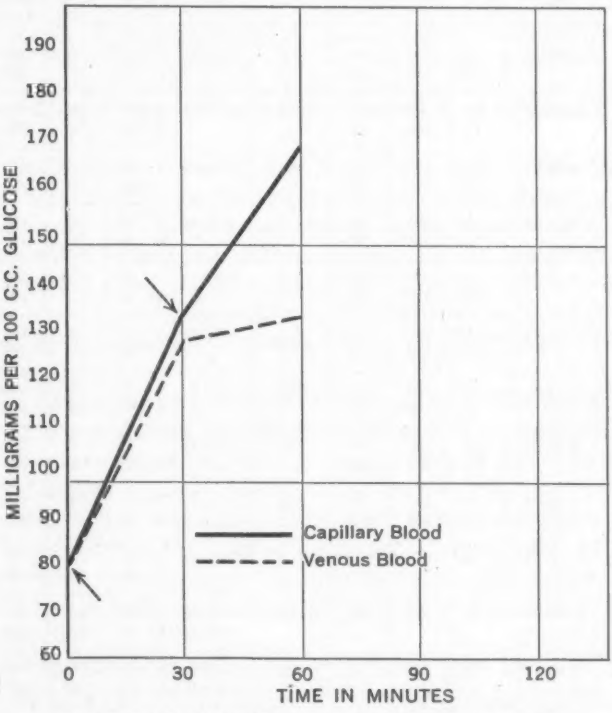
		Conventional 1-dose, 2-hour technique.					Exton-Rose 2-dose, 1-hour technique.				
	Subject.	Date.	Fasting, mg. per 100 cc.	½-hour, mg. per 100 cc.	2-hour, mg. per 100 cc.	Glycosuria, at 2 hr. %	Date.	Fasting, mg. per 100 cc.	½-hour, mg. per 100 cc.	1-hour, mg. per 100 cc.	Glycosuria, at 1 hr. %
1	L. D.	7-30-41	v 80 c 80	150 180	60 60	3.0	7- 3-41	v 100 c 95	163 190	180 230	4.0
2	J. G.	5-27-41	v 112 c 112	180 200	102 107	1.5	6-17-41	v 117 c 115	190 220	175 225	2.5
3	J. S. P.	4-28-41	v 113 c 110	175 190	100 95	Neg.	4-24-41	v 106 c 104	152 154	192 222	Neg.
4	J. R.	8- 1-41	v 85* c 95*	125 145	105 95	0.5	7-30-41	v 98 c 93	135 142	160 190	No report
5	E. B.	6- 2-41	v 97 c 100	176 190	123 123	1.0	6-23-41	v 90 c 90	170 173	180 190	2.0
6	H. R.	8-11-41	v 102* c 97*	176 198	189 197	5.0	6-16-41	v 92 c 95	160 165	166 178	1.0
7	W. M.	8-13-41	v 88* c 90*	155 168	105 112	Neg.	8-27-41	v 88 c 88	175 185	190 200	0.5
8	H. L.	6-11-41	v 100 c 102	130 164	125 145	Neg.	8-25-41	v 95 c 98	152 165	175 182	Neg.
9	J. P.	8-28-41	v 90* c 107*	150 186	95 115	Neg.	9- 4-41	v 85 c 90	150 155	160 181	Neg.
10	R. G.	11- 6-41	v 98*	173	115	0.5	10-30-41	v 82 c 85	155 174	175 210	0.3
11	R. O.	10-16-36	v 85	175	100	No report	4- 2-35 6-25-36	c 125 c 92	225 148	235 160	0.3 0.3
12	K. B.	3-25-40	c 70	145	75	Neg.	1-16-40 6-17-40	c 85 c 97	185 160	185 180	0.3 0.5
13	D. A.	11- 2-40	v 82* c 86*	128 192	81 114	Neg.	10-29-40	c 97	130	173	Neg.
14	R. C.	11-17-36	v 87*	118	72	Neg.	11-27-36	c 95	155	180	Neg.
15	A. B.	2-14-35	c 97	137	106	Neg.	2- 7-35	c 112	145	187	Neg.
16	D. C.	5-30-40	v 132	156	176	No report	5-22-40	c 110	150	175	2.0

v = venous blood glucose value. c = capillary blood glucose value.
* These subjects received 100 gm. of glucose in 325 cc. of water. All others received 50 gm. in 200 cc. of water.

Interpretation of Capillary Blood Values. Frequently in life insurance practice and in some clinical laboratories, capillary blood is employed instead of venous blood. We use venous blood by preference but the results obtained on capillary blood are included

in this paper as a matter of interest in some cases and because only capillary blood values were available in other cases.

The interpretation of results obtained on capillary blood is difficult, as one can surmise from the studies of Foster[6] and others, and it has been shown by Langner and Fies[10b] that when the results are not within normal limits, 2-dose tests on capillary blood may be misleading due to the unpredictable capillary-venous difference. This difference may be negligible or it may be over 50 mg. per 100 cc. This variation is not consistent and cannot be taken into account by any formula or selected conversion figures. Figure 1



Each arrow indicates the ingestion of 50 gm. of glucose.

FIG. 1.—Capillary-venous difference during the Exton-Rose procedure.

is included to illustrate the significant difference which may occur between simultaneous capillary and venous blood sugar values during the 2-dose test. Too often, the source of blood, whether it be capillary or venous, is not taken into account despite the fact that this may make a great deal of difference in the interpretation of results.

Results. In Table 1, even if one discounts the results obtained on capillary blood as misleading or unreliable, there are comparative figures on venous blood (designated v in Table 1) for each type of

glucose tolerance test. Let us confine our attention to the venous blood sugar values for the 2-dose test in the first 10 cases. According to the criterion of Matthews *et al.*[13] 2 subjects would be considered diabetic, 8 borderline, and none normal. According to the criteria of Gould *et al.*[7] all 10 individuals would be considered normal. According to the 1-dose test 7 subjects would be considered normal, 2 borderline, and only 1 diabetic. This comparison is summarized in Table 2.

TABLE 2.—SUMMARY AND INTERPRETATION OF RESULTS IN CASES 1 TO 10 IN TABLE 1.

	Normal.	Borderline.	Abnormal.
1-Dose Test.			
Venous blood sugar values	7	2	1
2-Dose Test.			
Venous blood sugar values—criteria of Matthews *et al.*	0	8	2
Venous blood sugar values—criteria of Gould *et al.*	10	0	0

In the last 6 cases of Table 1 only capillary blood sugar values are available for the interpretation of the 2-dose test. From our experience with capillary blood we would consider the first 2-dose test performed upon R. O. to be borderline, whereas the later test is normal. The tests in Cases 12 to 16 are all in the borderline range. According to the 1-dose test, Cases 11, 12, 13, 14 and 15 are clearly normal while Case 16 is diabetic. Case 15 (A. B.) first observed in 1935 (Table 1) is now a diabetic requiring insulin. Case 16 (D. C.) since his borderline 2-dose test in 1940 (Table 1) has been considered to be a mild diabetic.

To summarize the results we may say that in 3 out of 16 cases a borderline 2-dose test has accurately diagnosed diabetes; in 2 of these instances the 1-dose test was in agreement. In 13 cases an abnormal or borderline 2-dose test has occurred in presumably normal individuals; in 2 of these instances the 1-dose test was also borderline.

In 4 instances of borderline 2-dose tests we have augmented the test by giving a third dose of 50 gm. of glucose at the end of 1 hour. A representative result is depicted in Figure 2. In each instance a fall of the blood sugar value occurred following the third dose of glucose. It is highly probable, however, that the third dose of glucose has little or no influence on the configuration of the curve, in view of the fact that Warren, Karr, Hoffman, and Abbott[16] found the maximum rate of absorption of glucose from the gastro-duodenal unit to be 43.2 gm. per hour and usually it was considerably less than this. The first two 50-gm. doses in our 3-dose test would have been more than adequate to supply all the glucose that could have been absorbed in 2 hours so that the third 50 gm. would not be expected to cause additional absorption.

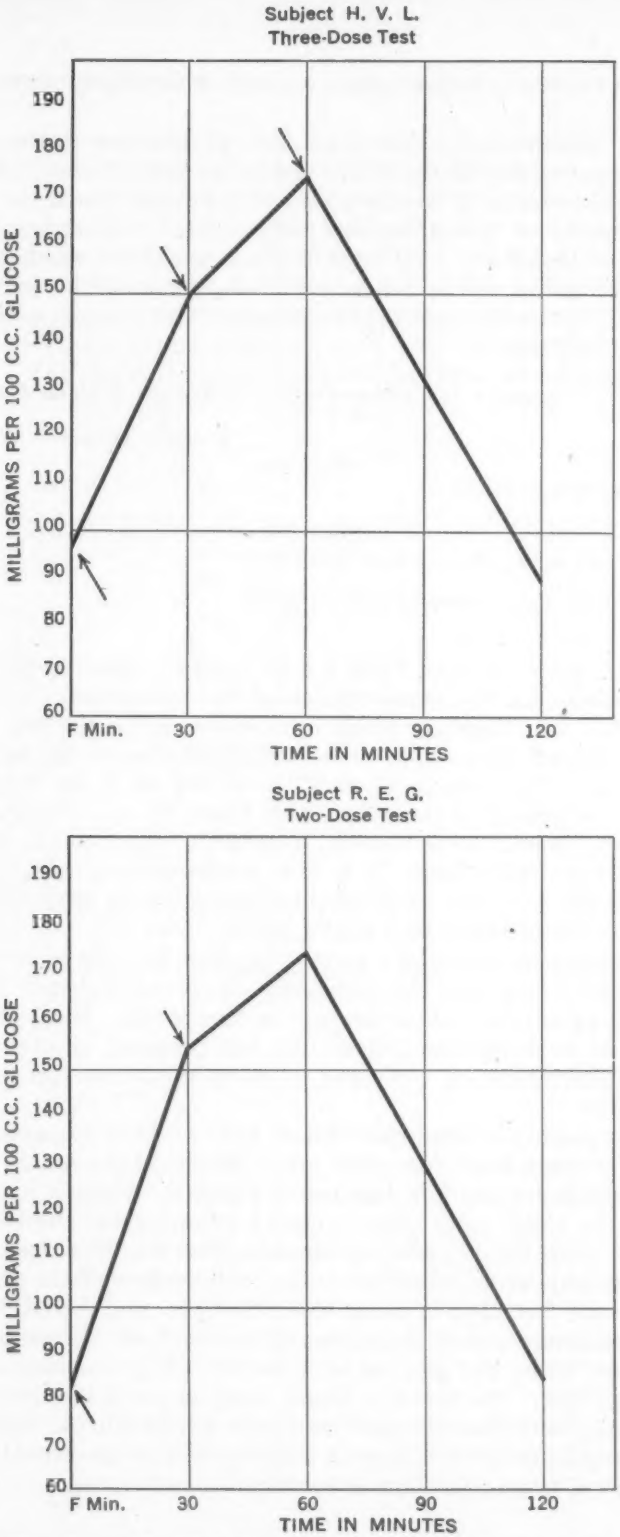


FIG. 2.—The response to multiple doses of 50 gm. of glucose given at ½-hour intervals. Each arrow indicates the ingestion of 50 gm. of glucose.

A second glucose tolerance curve is depicted in Figure 2 in which the Exton-Rose procedure is extended for 2 hours without the giving of a third 50 gm. of glucose. It will be seen that the two curves in Figure 2 are very similar whether 2 or 3 doses of glucose are given. This is not surprising since MacLean and de Wesselow[12] found that additional large doses of sugar given during the height of absorption failed to raise the blood sugar above the previous level. A pertinent question to which we plan to devote further study is a comparison of the effect of giving glucose in a single dose of 100 gm. or in divided doses upon the configuration of the resultant curves in the same individuals.

Comments. The results presented indicate that the 2-dose glucose tolerance test of Exton and Rose is usually more sensitive than the 1-dose test. We may draw one of two conclusions: either the 2-dose test is more accurate than the 1-dose test in detecting potential diabetes, or the 2-dose test is oversensitive and may be used as an exclusion test but in borderline cases should be rechecked by performing a conventional 1-dose test.

At this point we are inclined to believe that the 2-dose test of Exton and Rose possesses greater sensitivity but that the conventional 1-dose test is more specific for diabetes.

We have accepted the criterion of Matthews *et al.*[13] in interpreting our studies on the 2-dose test. Their criterion is more sensitive but less specific than the criteria of Gould *et al.*[7] We think it is wise to err on the side of safety and accept the more sensitive criterion. In accordance with this point of view, any individual with 1-hour blood sugar value in excess of 160 mg. per 100 cc. by the analytical method of Folin and Malmros or by the method of Folin and Wu should be suspected of having diabetes until proven otherwise. It is apparent from our study that there is a borderline range between 160 and 190 mg. per 100 cc. where the results may indicate either a normal state or diabetes; in this range prolonged observation may be necessary.

It is obvious from the results of the above discussion that the incidence of disagreement between the 2-dose and the 1-dose tests will depend partly upon the criteria used in interpreting these tests. Had we adopted the criteria of Gould *et al.* we should have considered the 1-dose test more sensitive than the 2-dose test.

In addition to the study which led to the establishment of the criteria of Matthews *et al.*[13] for the 2-dose, 1-hour glucose tolerance test, Dr. M. W. Matthews has also reviewed a large number of conventional 1-dose glucose tolerance tests at the Mayo Clinic and he has indicated to us in a personal communication that he considers the Exton-Rose procedure to be more accurate than the conventional 1-dose test in detecting diabetes, provided that the criteria established by Matthews *et al.*[13] are followed.

High diagnostic accuracy has been claimed for the Exton-Rose test in several series of cases.[4b,7,9,13] Our experience seems exceptional in that we have been able to find 13 cases out of 160 that have given what we consider to be borderline or abnormal Exton-Rose test when the 1-dose test and the clinical data suggest a normal carbohydrate metabolism. The above-mentioned 13 cases do not represent the total number of borderline Exton-Rose tests obtained in 160 consecutive tolerances. Additional instances of equivocal results were observed but only 16 could be studied sufficiently to supply material for this paper. It seems worthwhile to present our material because it demonstrates that the problem of interpreting the Exton-Rose glucose tolerance test is not infrequently just as difficult as the interpretation of the conventional 1-dose test, and because it indicates the need for more observation of the Exton-Rose test before final conclusions can be made regarding criteria, sensitivity and specificity.

Summary. From a group of 160 subjects who had submitted to the 2-dose, 1-hour glucose tolerance test, 16 cases are presented in which the results were borderline or slightly abnormal. A 1-dose test was also performed on these individuals. In 13 instances the 1-dose test and the available clinical data indicated a normal carbohydrate metabolism and therefore were in disagreement with the 2-dose glucose tolerance test. We believe that the conventional 1-dose glucose tolerance test is more reliable than the newer Exton-Rose procedure.

We wish to acknowledge the technical assistance of Harry L. Fies.

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STUDIES OF SUBSTITUTED VINYL BARBITURIC ACIDS.*

II. The Clinical Use of Sodium 5-Ethyl-5-(1-Methyl-1-Butenyl) Barbiturate (Vinbarbital Sodium).†

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In an earlier paper[8] detailed pharmacologic studies of 2 new substituted vinyl barbituric acids were described. These compounds were selected from a number synthesized by Cope and Hancock[5a–c] by their method for introducing alkyl vinyl groups into malonic and cyanoacetic esters. In animals the 2 new compounds were found to be effective narcotics with favorable characteristics. The more promising of the 2 was 5-ethyl-5-(1-methyl-1-butenyl) barbituric acid. It was found to have a comparatively wide margin of safety in rats and dogs and by comparison with isoamylethyl barbituric acid the "therapeutic index" of the new compound, as expressed by the LD50/AD50 ratio, was as great as, and perhaps greater than, that of the other barbiturate. The new compound also was found to be considerably less depressant to blood pressure upon intravenous and intraperitoneal injection in dogs than was the other barbiturate. Also some evidence was obtained indicating less profound depression of the respiratory center in decerebrate dogs from narcotic doses of the new barbiturate than from equivalent amounts of isoamylethyl barbituric acid. Only negligible amounts of narcotic material could be found in the urine of dogs after administration of anesthetic doses of the new compound. No significant degree of tolerance was developed in rats and dogs after repeated administration of the new drug and no toxic effects were observed in these animals which received repeated doses.

In view of the above findings, it was felt that the new barbiturate deserved preliminary clinical trial and the report of its administration as a sedative and hypnotic to approximately 100 patients was included in the earlier paper.[8] Results were good and no unfavorable reactions were observed. It is the purpose of this communication to report observations during more extensive clinical study of the compound. In addition to evaluating the usefulness of the barbiturate, the chief object of this study has been to watch for

* The first paper of this series was not numbered. It appeared under the title Studies of 2 New Substituted Vinyl Barbituric Acids (Ref. 8 in the bibliography of this paper).

† Vinbarbital sodium is the non-proprietary name which has been recognized by the Council on Pharmacy and Chemistry for this compound. The vinbarbital sodium used in this study was supplied by Sharp & Dohme under their trademarked name, "Delvinal Sodium."

toxic effects and undesirable reactions which might appear in a fairly large series of patients receiving the drug.

Following the favorable preliminary trial mentioned above the use of the new drug was continued at the Duke University Hospital. The sodium salt of 5-ethyl-5-(1-methyl-1-butenyl) barbituric acid (vinbarbital sodium) was administered in capsules by mouth to patients who needed an hypnotic or sedative. No attempt was made to use the new compound to the exclusion of other barbiturates and no restrictions were imposed upon the random selection of the cases, except precautions ordinarily observed in giving barbiturates.

During a 12-month experimental period, a total of 423 patients received the new barbiturate. The cases have been divided into five groups according to the number of doses each patient received. Those in Group I received only 1 dose and represent chiefly patients who needed only a single dose of an hypnotic while in the hospital. Many of these were in for a short stay. Also included are some cases in which a single dose was given for sedation before some minor procedure, such as sternal puncture or lumbar puncture. Patients in Group II received 2 to 5 doses, those in Group III 6 to 10 doses, Group IV 11 to 20 and Group V more than 20 doses. To the above series of 423 cases have been added 42 others collected after the first 12-month period but followed carefully because of some point of special interest in the case. These have been divided among the groups in the same manner. Because the medical service on which the drug was used is a very active one, with rapid turnover of patients, the opportunity was not available for long-continued administration of the drug in the majority of patients. However, a considerable number of cases is included in Groups IV and V and most of those in Group V received comparatively large amounts of the drug.

Patients who received the new barbiturate were observed for evidence of undesired or toxic reactions, such as excessive depression, undue persistence of drowsiness, excitement, nausea, dermatitis, and so on. In addition, the case record of every patient was reviewed in a search for possible toxic effects. In most patients who received more than 1 dose of the drug, blood counts and urinalyses done before and after the administration of the drug were compared in looking for evidence of hemolytic anemia, suppression of bone marrow activity or irritation of the kidneys which might have been caused by the barbiturate. This information was available on all cases in Group V, all except 3 in Groups IV and III and in 73% of cases in Group II. Failure to record the information after the drug was given in the rest of the cases in Group II usually was due to the brief duration of the patient's stay in the hospital. Blood and urine examinations were checked, if recorded, before and after the drug on patients in Group I (who had only 1 dose) and all

of the case histories were reviewed so that any important toxic reaction would have been detected.

Table 1 presents a summary of the cases used, divided according to diagnosis, and indicates the number of cases of each general diagnosis included in the various groups mentioned above. In the interest of brevity diagnoses have been stated in general terms and cases have been classified only according to the chief condition or disease.

TABLE 1.—ANALYSIS OF CASES USED.

Diagnosis.	Number of cases in each group. Groups.					
	I.	II.	III.	IV.	V.	Total.
Asthma and allergic states (except skin conditions)	7	10	2	3	4	26
Diseases of the blood (including anemias, leukemias, etc.)	14	12	1	3	..	30
Diseases of bones, joints and cartilage (including arthritis)	3	12	4	1	1	21
Deficiency states	1	5	..	..	1	7
Diabetes mellitus	7	11	1	1	1	21
Fevers	8	2	1	..	1	12
Fungus diseases	1	..	..	1	..	2
Gall bladder diseases	4	4	..	2	..	10
Diseases of heart and blood-vessels	21	24	5	5	5	60
Diseases of kidney and urinary tract	3	2	3	..	..	8
Lead poisoning	1	..	..	..	..	1
Liver diseases	1	3	1	1	..	6
Lung diseases (except tuberculosis)	7	13	1	2	..	23
Diseases of the nervous system (including psychoneurosis)	23	31	2	2	1	59
Skin diseases	6	6	2	1	..	15
Diseases of stomach and intestines	14	5	3	4	1	27
Syphilis	10	8	1	1	6	26
Diseases of throat and nose	3	7	2	..	..	12
Thyroid diseases (chiefly hyperthyroidism)	5	14	3	3	19	44
Tuberculosis	7	6	4	3	1	21
Tumors (benign and malignant)	6	10	5	4	1	26
Diagnosis deferred	3	5	..	..	..	8
Total	155	190	41	37	42	465

Dosage and Uses. For medical patients vinbarbital sodium has been given in doses of from 32 mg. (½ gr.) to 0.2 gm. (3 gr.). The average dose and the one used in the great majority of cases was 0.1 gm. (1½ gr.). Single doses of more than 0.2 gm. (3 gr.) have been given therapeutically only on rare occasions in our series. However, in studying the effect of the drug on blood pressure, respiration and heart rate (as described below), a number of patients were given 0.3 gm. (4½ gr.) as a single dose, without harmful effects. In cases where profound sedation was desired 0.2 gm. doses were repeated at intervals of about 2 hours until the desired effect was obtained. The largest amount so given in 24 hours was 1.4 gm. (21 gr.) to a patient with extensive chronic bronchitis and intractable asthma.

It is felt that average doses mentioned above are quite conservative and that with proper precautions larger doses could have been used with safety if they had been indicated. Indeed, Davidoff[6] and Davidoff and Goodstone[7] have reported the frequent use of doses of the order of 0.3 to 0.6 gm.

(4½ to 9 gr.) in disturbed patients without significant untoward effects. Occasionally they gave, in divided doses, amounts ranging from 1.3 to 2 gm. (20 to 30 gr.) in severely excited individuals. The administration of very large doses of this or similar compounds should be undertaken only under conditions permitting careful observation of the patient and only by those familiar with the management of possible complications.

The widest use of the drug on the medical wards has been for administration at bedtime as an hypnotic to patients with simple insomnia. Here the dose usually was 0.1 gm.; occasionally 64 mg. (1 gr.) or 0.2 gm. The smaller doses were repeated after 2 to 3 hours, if the first dose was not effective or of too short duration.

A number of patients in need of continued sedation also have been given vinbarbital sodium in doses ranging from 32 mg. 2 or 3 times per day, in mildly nervous individuals, to 0.1 gm. 3 or 4 times per day in cases of severe hyperthyroidism. Perhaps special mention should be made of this later usage. Twenty-two cases of hyperthyroidism received the drug in repeated doses, particularly postoperatively, for the control of nervousness and as an adjunct to other standard therapeutic measures. The dosage employed usually was that mentioned above but occasionally 32 mg. t.i.d. and 0.1 gm. at night was sufficient. Results were gratifying, especially in 3 very severe cases where the control of nervousness and hyperactivity was of utmost importance. It was the particular observation of both the medical and surgical attendants that these symptoms were controlled adequately without the production of undue depression or somnolence. None of the cases showed any indication of toxic effects of the drug. Fifteen other less severe cases of hyperthyroidism received the new barbiturate in smaller doses.

To allay anxiety, and as sedative preparation for minor procedures, such as lumbar puncture or sternal puncture, doses of 0.2 gm. have been given about 1 hour before the procedure was to begin. It is preferable in such instances to allow 1 hour for the full development of the effect of the drug.

Vinbarbital sodium also has been used in conjunction with coal-tar analgesic drugs to increase the effectiveness of the latter in relieving pain. Here the dose has been 32 mg. to 0.1 gm., together with the usual dose of salicylate or phenacetin, and the combination is particularly effective in combating mild or moderately severe pain associated with considerable nervous tension. No attempt has been made to relieve pain with vinbarbital sodium alone, because it is not to be expected that such a drug will have pronounced analgesic effects unless given in comparatively large doses, as in obstetric amnesia.

Results. The results of experience with the new barbiturate may be summarized briefly by the statement that the drug has been found to be an effective hypnotic and sedative with very desirable characteristics; and that few unfavorable reactions have occurred following its use.

In observing the patients and reviewing the case histories summarized in Table 1, particular search was made for unexplained falls in hemoglobin, red cells or white cells in the blood; the occurrence of purpuric manifestations; and the appearance of albumin, casts or red cells in the urine, following the use of delvinal sodium. All cases showing a fall in hemoglobin of more than 10% were investigated but in every instance the fall was readily explainable on the basis of the patient's disease. No cases receiving the drug

developed leukopenia or evidence of thrombocytopenia, and 1 patient with preëxisting leukopenia received it as a sedative without exaggeration of the condition. No abnormalities in the urine, which had not been present previously, were found following the drug.

Evidence of the development of toxic hepatitis following the new barbiturate also was sought for but not found in any case. Three patients with such liver damage due to sulfonamide drugs received vinbarbital sodium without evidence of harm from it. One of these patients, who also had Hodgkin's disease, died after leaving the hospital. The other 2 recovered before discharge. It should be mentioned that the effect of barbiturates is apt to be increased in the presence of liver damage[3,9,10] and that they must be used with due caution under such circumstances.

Concerning untoward effects of the drug comparatively little can be said because of the scarcity of such reactions. The nearest approach to a serious reaction was in a 66-year-old white widow with generalized arteriosclerosis, arteriosclerotic heart disease with auricular fibrillation, pernicious anemia, diabetes mellitus and chronic cystitis. Approximately 10 hours after 0.1 gm. of the drug the patient was slightly confused and probably dizzy, because she fell while getting out of bed. However, she had received for the cystitis, 1.8 gm. of sulfanilamide per day for 3½ days before the dose of barbiturate was given. In view of the time intervals and the well-known effect of sulfanilamide in causing confusion, dizziness, and so on, it seems probable that it was the chief offender in this case. However, it has been reported that barbiturates are rendered more toxic by sulfanilamide[1,2] and it is possible that the small dose of the barbiturate may have contributed to the reaction because of the simultaneous administration of sulfanilamide. It may be mentioned at this point that patients receiving sulfonamides may be more susceptible to the action of barbiturates.

One 27-year-old white male developed an itching vesicular and papular rash, associated with mild pharyngitis, at first thought to be chickenpox, later regarded as "possibly a drug eruption"; 2 days after the second of 2 consecutive nightly doses of 0.1 gm. of vinbarbital sodium. The rash cleared within 3 to 4 days and its nature was not definitely determined. The patient had received atropine 2 days before and atropine and prostigmine on the day the rash appeared. This may represent a case of drug rash due to vinbarbital sodium, but the evidence is inconclusive. No other similar cases were observed. The drug was used for sedation in a number of cases of skin diseases with exaggeration of symptoms in only 1 case. This was a 41-year-old white man with severe dermatophytosis of the feet and extensive dermatophytid reaction. There was a moderate flare-up of the latter process, with increased itching, following a single dose of 0.3 gm. (4½ gr.) of vinbarbital sodium which was given to observe the effect on blood pressure, and so on,

as reported below. It was discovered later that the patient had reacted similarly to phenobarbital.

Excitement was not observed following the use of vinbarbital sodium and only 1 abnormal psychic reaction was seen. It is unlikely that this was related to the drug. A psychoneurotic, 39-year-old white spinster, who was prone to have hysterical attacks, received 0.2 gm. of the drug for sedation at night following lumbar puncture. She slept during the night but was found the following morning in a detached mental state which the psychiatric consultant viewed as an episode of dissociation hysteria. It was his opinion that this represented an exaggerated reaction related to the patient's hysterical tendencies, probably precipitated by the lumbar puncture, and that the use of the barbiturate was only incidental. The patient returned to her normal state after about 8 hours.

It is recognized that excitement is not likely to occur following barbiturates among patients such as were used in this study. However, the freedom from reactions of this type in our cases has been gratifying and Davidoff and Goodstone[7] have reported comparatively few untoward reactions in psychiatric patients who were treated with vinbarbital sodium. Nausea or other gastro-intestinal complications were not observed in our patients following the drug.

There was no clinically detectable evidence of habituation to the drug under the conditions of hospital administration. It was given to some patients who required repeated sedation with it or some other sedative; but nothing was seen to indicate any special attachment to or craving for this particular drug in any of the patients. So far as could be determined tolerance was not developed. When the barbiturate was given repeatedly as an hypnotic to patients with simple insomnia the dose was not increased after repeated administration and we were not able to detect that the drug lost its effectiveness in these cases. However, our cases were not well suited for investigation of tolerance because the drug was not continued for long periods of time in most of them. Davidoff and Goodstone[7] have reported less tolerance to vinbarbital sodium after repeated administration than to two other commonly used barbiturates. These observations are in accord with the findings reported in the previous paper,[8] concerning the relative lack of tolerance in rats and dogs, as judged by the average dose of the drug necessary to continue to narcotize the majority of a group of animals after repeated administration. However, Carmichael and Thompson[4] have reported a decrease in the sleeping time of guinea pigs after repeated administration of a fixed dose of vinbarbital sodium.

Considerable clinical experience with the drug has produced the impression, consistent with the results of experimental work in animals, that vinbarbital sodium definitely belongs to the group of so-called "short-acting"[11] barbiturates. On the basis of both experimental and clinical observation, it appears that its action is of shorter

duration than that of sodium amytal. In addition, while reliable comparative clinical information is difficult to obtain, the definite impression has been gained from observation of patients that in average dosage the new drug also is briefer in its effects than sodium pentobarbital.

The induction of sedation with vinbarbital sodium appears to be somewhat slower than with sodium pentobarbital. The induction time for sleep, when the drug is given about 3 to 4 hours after the evening meal, usually is of the order of 30 to 35 minutes. Induction appears to be quite gradual and patients have not complained of the "drugged sensation" during induction with this drug which occasionally is experienced with other commonly used barbiturates. The absence of this sensation, after taking vinbarbital sodium, has been the subject of spontaneous comment by several individuals with better than average powers of observation, who were asked to try the drug and who usually had experienced the sensation after other barbiturates.

When vinbarbital sodium is given at bedtime to patients with simple insomnia who have no stronger stimuli than nervousness or mild anxiety to keep them awake, and whose chief difficulty is in going to sleep, the usual experience is that they will sleep until awakened the following morning by the activities of the ward. In patients who have some definite discomfort or stimulus which might be expected to awaken them when the sedative effect of the drug reaches a low level; sleep usually lasts, with average doses, for 3 to 5 hours, there being, of course, much variation among individuals. Greater duration of action results as the dose is increased.

Persistence of drowsiness beyond the time of normal awakening, or "hangover," following average doses has been so rare as to make doubtful the significance of the subjective sensations of this type described by the few patients who have mentioned them in response to leading questions. Such symptoms undoubtedly have been present when patients were awakened within 2 to 3 hours after receiving the drug and prevented from going back to sleep by examinations, treatment, and so on; and in individuals who were given repeated doses with the deliberate purpose of producing prolonged sedation.

Effect on Blood Pressure, Pulse and Respiration. To observe the effect of the new barbiturate on blood pressure, pulse and respiration 25 patients in good general condition were given larger than average doses and followed with care for 2½ to 3 hours, or until any depression which had been observed largely had disappeared. The doses used for routine administration were so small as to make unprofitable an attempt to follow in this fashion every patient who received the usual therapeutic dose of 0.1 gm. The 25 patients were given at 1 dose 0.2 or 0.3 gm. (3 or 4½ gr.), roughly according to body weight, and readings were taken at intervals of ½ hour. Fourteen

patients received 0.2 gm. and 11, 0.3 gm. There was no significant difference in the two groups. After the drug was given the mean change in blood pressure in mm. of mercury for the 25 patients was: at 1 hour, −3 systolic and −3 diastolic; at 2 hours, −5 systolic and −4 diastolic; and at 2½ or 3 hours (all except 6 followed 3 hours), −3 systolic and −2 diastolic. In only 4 cases was there observed a fall of more than 10 mm. of mercury at any time and in only 2 or more than 20 mm. (24 and 22 mm. respectively). Both of the latter were in patients who had been made apprehensive by the repeated blood pressure readings to establish a base line before the drug was given and whose starting pressure, therefore, was above their normal range.

The mean change in pulse rate per minute was: at 1 hour, −2; at 2 hours, −5; and at 2½ or 3 hours, −4. In no case was there observed abnormally fast or unusually slow heart rate following the drug.

The average respiratory rate did not change at 1, 2 or 3 hours following the drug and no significant change of rate was observed in any patient. It is believed that there was no change in blood pressure, pulse or respiration in any of the 25 patients which would indicate undue depression by vinbarbital sodium. Nor have we observed any other evidence of such untoward effect from doses of the drug which have been needed in our patients. Davidoff and Goodstone[7] in giving large doses of barbiturates to excited patients observed more frequent lowering of systolic blood pressure, but much less frequent respiratory depression, with vinbarbital sodium than with sodium amytal or pentobarbital sodium.

Pathologic Studies. Seventeen patients who received vinbarbital sodium died in the hospital and 2 are known to have died after discharge. Autopsy was performed in 11 of these cases. Only 3 patients who died received more than 5 doses of the drug, 1 receiving 6, another 7 and the other 21. Deaths were due to a variety of causes but all were readily explained by clinical or autopsy findings. Careful review of the case history in every case failed to furnish any evidence that the drug contributed in any way to the fatal outcome.

In addition, the writer is indebted to Dr. D. H. Sprunt for reviewing the histologic sections of the organs of 10 autopsies (1 autopsy was done outside the hospital and the material was not suitable for microscopic examination). No abnormalities were found in any case which could be interpreted as due to toxic effect of the barbiturate.

Summary. A new barbiturate (vinbarbital sodium), which showed very favorable characteristics during experiments on animals, has been administered to a series of 465 patients under hospital observation. The compound was found to be an effective sedative and hypnotic when used in a wide variety of disease states. No serious and few undesirable reactions were encountered. The usual

dosage was from 32 mg. (½ gr.) to 0.2 gm. (3 gr.). The new drug belongs to the group of so-called "short-acting" barbiturates, its effect is gradual in onset, relatively brief in duration and seldom persists beyond the time of natural awakening. No significant effects on blood pressure, heart rate or respiratory rate were produced by larger than average doses. In 10 cases which came to autopsy after having received the new barbiturate, no lesions were found which could be interpreted as due to toxic effect of the drug.

Because of the results of animal experimentation and the experience described above during its administration to patients, it is believed that the new barbiturate represents a worthy addition to the list of sedative drugs available for clinical use.

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GASTROSCOPIC OBSERVATIONS IN PULMONARY TUBERCULOSIS.*

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It is well known that tuberculous enteritis is a common complication of cavernous pulmonary tuberculosis. Tuberculosis of the stomach, however, is very rarely found. Cullen[1] found at autopsy, that 70.4% of 1043 cases of pulmonary tuberculosis had tuberculous lesions involving the mucosa of the small intestine and colon; but was able to find only 4 cases of tuberculous involvement of the gastric mucosa. It should be pointed out, however, that gastric symptoms are not infrequently present in patients with advanced

* Opportunity to study these patients was made possible by the coöperation of the Tuberculosis Service.

TABLE 1.—ANALYSIS OF DATA.

Patient.	Age.	T.B. status.*	Diagnosis secondary.	Sputum. For T.B.	Sputum. Amount.	Gastric. For T.B.	Gastric. Acidity.	Duration (yrs.).	G.I. symptoms.	Gastroscopic diagnosis.
W. C.	48	3B	Pul. fibrosis	+	Mod.	?	+	2–3	Anorexia	Normal stomach.
W. C.	64	1A	Pul. fibrosis and emphysema	0	Mod.	?	No res.	½	Diarrhea; melena	Normal stomach.
V. M.	78	3B	....	+	Mod.	+	+	4	Anorexia; hematemesis	Normal stomach.
L. R.	34	3C	....	+	Profuse	0	No res.	½ (1?).	None	Normal stomach.
G. L.	34	3B	Tb. bronchus	+	Scant	0	0	9	Gas. distention (G.B. neg.)	Normal stomach.
I. H.	21	3B	Artif. pneumothorax	+	Scant	?	0	1	Hematemesis, N. and V.	Chr. superf. gastr., with hem.
J. N.	38	3B	Latent syphilis	+	Mod.	?	0	1½	Anorexia	Chr. superf. gastr.
R. S.	36	3B	Syphilis	+	Mod.	?	0	4	None	Chr. superf. gastr.
T. G.	28	2B	Chr. alcoholism	+	Scant	+	+	½	None	Chr. superf. gastr.
F. J.	43	2B	Artif. pneumothorax	+	Scant	0	+	1	Diarrhea (neg. G.I. roentgen ray)	Chr. superf. gastr., with hem.
T. McM.	24	3B	Tb. enteritis	+	Mod.	+	+	2	Vomiting, cramps, diarrhea	Chr. superf. gastr., with hem.
J. F.	46	3B	Tb. bronchus	+	Mod.	?	No res.	20	Anorexia	Chr. superf. gastr.
B. C.	47	3B	Carc., alcoholism, pul. fib. and emphysema	0	Mod.	?	No res.	9	None	Chr. atr. gastr.
B. N.	27	3C	Tb. enteritis	+	Mod.	+	0	½	Eructations; upper abd. distress	Chr. atr. gastr.
L. M.	36	3C	Syphilis	+	Profuse	?	0	¼–½	None	Chr. atr. gastr.
J. F.	46	3B	....	+	Mod.	?	+	1	None	Chr. superf. gastr.; marked chr. atr. gastr.
McC.	41	2B	Tb. enteritis (?)	+	Mod.	?	No res.	¼	Epigastric and low abd. pains	Chr. atr. gastr.; chr. superf. gastr., antral distortion.
W. G.	21	3B	Asthma and tb. laryngitis	+	Mod.	0	0	½	None	Chr. atr. gastr.; chr. superf. gastr.
J. D.	49	3B	Seronegative syph. (treated)	+	Profuse	?	0	½	Anorexia; constipation	Chr. atr. gastr.; chr. superf. gastr. (antrum).
A.F.	38	2C	Laryngitis syph., artif. pneumo.	+	Scant	?	0	1/12	Anorexia; vomiting	Chr. superf. gastr.; chr. atr. gastr.
A. R.	29	2B	Phlyct. conjunctivitis	0	None	0	0	¼	Upper abd. pain unrelated to meals	Chr. atr. gastr.; chr. superf. gastr.
J. C.	40	2B	Tb. peronitis	+	Mod.	0	0	1	Prev. intest. obstruction	Chr. atr. gastr.; chr. superf. gastr.
J. F.	37	3B	Tb. bronchus, tb. enteritis	+	Mod.	?	No res.	4	Cramps; diarrhea	Chr. superf. gastr.; chr. atr. gastr.
J. C.	41	3B	Silicosis	+	Mod.	?	No res.	4	Epigastric distress; tender; distended; gas.	Chr. atr. gastr.; chr. superf. gastr.
J. L.	27	3C	Tb. laryngitis; tb. enteritis	+	Profuse	+	No res.	¼	Cramps; diarrhea and constipation	Chr. superf. gastr.; chr. atr. gastr
T. B.	42	2B	Drug addiction	+	Profuse	0	+	4	None	Chr. hypertrophic gastritis.

* Tuberculous diagnosis: 1. Minimal. 2. Moderately advanced. 3. Far advanced. A. Asymptomatic. B. Minimal to moderate symptoms. C. Marked symptoms.

pulmonary tuberculosis. He found that 29.3% of the patients had digestive disturbances. The gastric symptoms encountered consisted of anorexia, pain, nausea, vomiting and belching.

Renander,[3] in a recent publication, reported 2 cases of proven tuberculosis of the stomach, and reviewed the small number of reported cases. It is notable that the majority of these develop on a basis of a hematogenous dissemination to the stomach wall, or, more frequently, to adjacent structures—particularly lymph nodes. There are not roentgenographic findings pathognomonic of tuberculosis of the stomach. Tuberculous lesions of the stomach may cause plyoric stenosis, in which case it is secondary to healing by fibrosis and cicatrization of an antecedent annular ulcerative lesion. They may resemble infiltrative neoplasms, as well as polypoid gastritis. No cases diagnosed by gastroscopy have been reported.

No gastroscopic observations in tuberculous patients have come to our attention. While the effect of a chronic debilitating disease on the gastric mucosa may be due to several factors, among them deficient absorption or increased requirement of vitamin, several questions of special interest arise in the tuberculous patient.

Materials and Methods. In this investigation 27 patients with pulmonary tuberculosis were gastroscoped. This study was undertaken in an effort to clarify three points: First—can a specific lesion be demonstrated in the stomach in late stages of pulmonary tuberculosis if the gastric mucosa is examined through the gastroscope? Second—what effect has the prolonged swallowing of purulent material on the gastric mucosa? Third—could the gastroscopic findings be correlated with the presence or absence of digestive complaints?

The patients selected for examination all had severe pulmonary disease of a few month's to 20 years' duration. Many were in the advanced stages of tuberculosis. The gastroscopist did not know whether gastric symptoms were present until the final tabulation of results was completed.

Results (Table 1). While none of the 27 patients examined was ambulant, and some were so weak that it was necessary to lift them from stretcher to examining table, 26 were successfully gastroscoped.

Entirely normal gastric mucosa was encountered in 5 patients. Chronic superficial gastritis was found in 7; chronic atrophic gastritis in 3; and a combination of these lesions occurred in 10 patients. Chronic hypertrophic gastritis was seen in only 1 patient. Ulcers, tumors and tuberculous lesions were not observed. Mucosal bleeding was seen in 3 of the patients with chronic superficial gastritis.

The 5 patients in whom normal gastric mucosæ were found had no gastric complaints except anorexia. Ten of the remaining 21 patients had diffuse involvement of the gastric mucosa of a moderate to marked degree, but only 3 had gastric symptoms, while 6 of the 11 patients with only patchy, mild to moderate mucosal involvement had gastric complaints.

Symptoms occurred in 6 of the 10 patients having both chronic

* Tuberculous diagnosis: 1. Minimal. 2. Moderately advanced. 3. Far advanced. A. Asymptomatic. B. Minimal to moderate symptoms. C. Marked symptoms.

superficial and atrophic gastritis, in 2 of the 7 patients with chronic superficial gastritis, and in 1 of the 3 patients with chronic atrophic gastritis. The one patient with chronic hypertrophic gastritis had no gastric complaints.

The sputum varied in amount from scant to profuse, a moderate amount representing the average. Tubercle bacilli were present in the sputum of all but 3 patients. The fasting gastric contents usually were slight in amount, and 8 patients had no residue. Of the remaining 19 patients only 7 had free hydrochloric acid in the fasting specimen. In 9 patients the gastric residue was examined for tubercle bacilli which were present in 5, 3 of whom had free hydrochloric acid in the specimen.

Discussion. No apparent correlation between duration, severity, or type of tuberculosis and the presence of abnormalities of the gastric mucosa could be found. Neither could the amount of sputum produced be directly correlated with involvement of the gastric mucosa. The quantity of sputum swallowed could not be measured.

No specific gastric lesion was encountered gastroscopically. The absence of a specific gastric lesion is of particular interest since 5 of the patients had tuberculous enteritis. Chronic superficial gastritis was found in about double its incidence in patients with gastric complaints but no systemic disease.[2,4] The progression of this mucosal alteration to chronic atrophic gastritis was seen in a correspondingly large group of patients. Whether these findings are caused by swallowed purulent material or general debility of the patients cannot be determined until comparable studies in other debilitating diseases are carried out.

Nine of 21 patients with gastroscopic evidence of abnormal mucosa had digestive symptoms, while none of the 5 patients with normal findings had such complaints. All of these patients had scant fasting gastric contents, and in only 7 of the entire series could free hydrochloric acid be found. The low incidence of gastric complaints in the patients with abnormal mucosæ may be explainable by the fact that all were at bed rest, most ate sparingly, and hydrochloric acid was frequently absent from the fasting gastric specimen. Cullen[1] reported an incidence of digestive symptoms of 21.7% in tuberculous patients without specific intestinal lesions. This relationship corresponds closely to our observations and the presence of non-specific gastritis may have been related to this portion of Cullen's[1] series.

Summary. Twenty-seven patients with pulmonary tuberculosis had gastroscopic examinations made.

No specific lesion was found, even though 5 patients had tuberculous enteritis. Chronic superficial gastritis was found alone and combined with chronic atrophic gastritis in an unusually large number of patients. The abnormalities of the gastric mucosa, how-

ever, could not be correlated with the duration, severity, or type of tuberculosis, nor with the quantity of sputum expectorated.

Gastric symptomatology failed to follow directly the gastroscopically demonstrated lesions; but this was thought to be influenced by bed rest, the reduction in food consumption caused by anorexia, and frequent absence of free hydrochloric acid in the fasting specimen.

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AN UNUSUAL CASE OF AMEBIC HEPATITIS.

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Case Abstract. A male, negro, elevator operator, aged 32, who was born in New Orleans and had lived in Mississippi until 1938, was admitted to this hospital, February 17, 1941. The chief feature of his past history was that his bowels usually moved 3 or 4 times a day; they were quite loose and occasionally contained bright red blood. Five days before admission he developed a head cold with some pain in his chest and abdomen. Later, the pain became sharp in the upper back, right flank and right lower quadrant, gradually involving the entire abdomen and radiating into the scrotum. There was no diarrhea, chills or urinary symptoms. Temperature on admission was 102°, his white blood count 14,000 and polys 66%. Urine contained albumin and an occasional red blood cell. There was marked tenderness in the right costovertebral angle extending around the flank to the right lower quadrant, associated with spasticity, but no rebound tenderness. The rectum was tender high up on the right side.

Films of the kidneys and urinary tract showed no abnormality. Analyses of urines subsequently were negative. A diagnosis of "appendicitis and possibly pyelonephritis" was made.

Laparotomy on the night of admission revealed no fluid in the abdomen. A pale but slightly injected appendix was removed (pathologic report normal). The mesenteric nodes were not enlarged. Culture of peritoneal fluid was sterile.

Subsequent Course. During the first few days after operation the temperature ranged between 101° and 102°. He vomited several times and his abdomen was distended. A Miller-Abbott tube was inserted, the Roentgen ray having shown marked distention of the jejunum and ileum with fluid level formation.

On the fifth day after operation his scleræ became icteric and there was considerable tenderness over the liver and right costovertebral angle and some bulging in the right upper quadrant. The history of loose stools, passage of blood, the presence of jaundice and tender liver suggested a stool hunt for amebæ, and these were found within a short time. At this time his temperature rose to 104°. There was dullness and diminished breath sounds over the right base, that is, signs of fluid, and marked tenderness over the right costovertebral angle and over the liver though the edge of this organ could not be felt.

Emetine hydrochloride, 0.06 gm., was begun 8 days after operation and continued for 2 weeks. During this period the temperature never rose above 101°, and tenderness of the liver had almost disappeared. Three days after stopping emetine the temperature rose to 104° and a second course, lasting 1 week, was instituted. Anayodin by mouth was also administered to destroy the intestinal parasites. Owing to relapse of fever a third course of emetine, lasting 15 days, was begun, and 54 days after operation 400 cc. of straw-colored, hazy fluid was withdrawn from the right pleural cavity. Guinea pig inoculation and culture of this exudate were negative. His convalescence from this point was gradual, but complete; repeated examination of stool was negative, and all physical signs of illness disappeared.

Discussion. Mistaking amebic intestinal disease for appendicitis is not new; it has been described repeatedly during the recent Chicago epidemic, and is probably due to ulceration of the cecum.

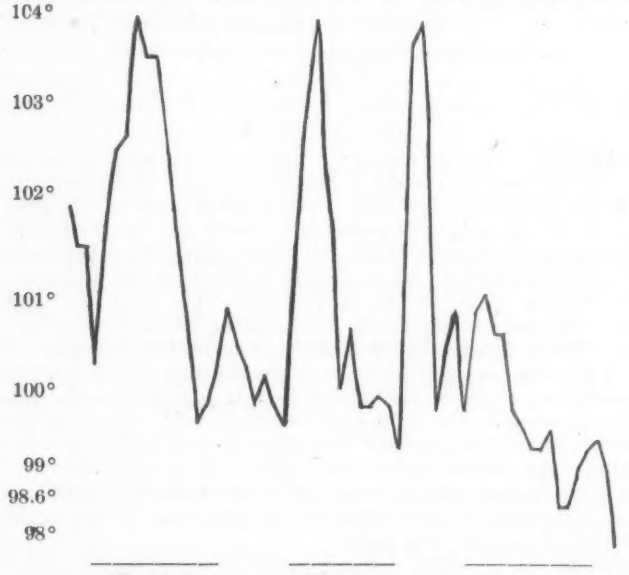

CHART 1.—The effect of emetine on the temperature in a case of amebic hepatitis.

The costovertebral tenderness and radiation into the groin and scrotum were probably due to pressure on or irritation of the right urinary structures by the diseased liver according to the urologic consultant. The intense jaundice is also rare in amebic disease of the liver. The late Professor O'Connor, who had a large experience with amebic liver abscess in the tropics, stated that jaundice in liver abscesses was rare. In this case the bilirubin reached 18 mg. per 100 cc. and was associated with a low phosphatase. The negative cephalin flocculation test is also remarkable.

The necessity for three courses of emetine is unusual. Ordinarily one course suffices, but as there was a prompt rise in temperature (see Chart 1) following withdrawal, we preferred to repeat its administration until a more lasting effect was procured. Being

aware of the toxic effect of the drug on the heart, we were on the lookout for cardiac signs, and rather concerned because of the relatively large size of the total dose and its well-known cumulative effect. Perusal of the literature leads me to conclude that should another opportunity arise, I would control its use by periodic electrocardiograms.

With regard to the blood chemistry (see Table 1) the low total cholesterol and the abnormal ester to free ratio in the early period followed by a return to more normal figures is interesting. The normal phosphatase with a serum bilirubin of 18.7 at the outset and the gradual increase of the former as the latter decreased is also of interest. I am unable to offer a satisfactory explanation.

TABLE 1.—BLOOD CHEMISTRY DATA.

Date, 1941.	Plasma cholest.	Phospha-tase.	Bilirubin.	A/G ration.	Ceph. test.	NPN, mg.
2/22	..	3.7	18.7	..	Neg.	
2/25	64 (F—42, C—24)	2.3				
2/27	..	4.7				
3/1	..	5.7	12.5	A = 3.1 = 1.4 G = 2.2	Neg.	50
3/5	..	..	3.9			
3/7	146 (F—47, C—99)	10.1				
3/24	150	..	0.9			
4/14	..	11.1	Tr.			

The white count was elevated to around 15,000 throughout the illness with a relatively high neutrophil count.

Summary. 1. Acute abdominal symptoms and signs associated with fever and leukocytosis were erroneously diagnosed as appendicitis.

2. Removal of a normal appendix was followed by jaundice, abdominal distention, tenderness over the liver and fluid in the right chest. A low serum phosphatase was associated with high serum bilirubin.

3. Amebæ were found in the stool.

4. Three courses of emetine administration were necessary to effect a cure of the amebic hepatitis.

AN ACUTE PERFORATED DUODENAL ULCER FOLLOWING METRAZOL THERAPY.

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THE rare occurrence of an acute perforated duodenal ulcer following 1 week after metrazol treatment merits some consideration beyond assuming that it is mere coincidence. Recently, Moore

and Friedman[11] reported 2 cases of ruptured duodenal ulcer in young adult males occurring 9 to 17 months respectively after metrazol injections. They suggested that although considerable time had elapsed since the metrazol treatment had been instituted, in view of the neurogenic theory of the origin of peptic ulcers, pathologic changes in the brain or a disturbance of the autonomic nervous system may have been sufficient to initiate the ulcers. DeBakey[5] reviewed the subject in general of acute perforated gastro-duodenal ulceration and Vonderahe[19] discussed the various theories dealing with the cause of peptic ulcers, particularly from the neurogenic viewpoint. Stender,[18] Reitmann[14] and Liebert and Weil[9] studied the effect of metrazol on the nervous system. Roback and Miller[15] found subarachnoid and intracranial hemorrhages following 9 injections of metrazol. Hassin[7] found nerve cell changes in a patient who had metrazol injections preceded by insulin shock treatment. From studies on dogs and rabbits, Whitehead *et al.*[20] suggested that the pathogenesis of the brain lesions is due to the anoxemia resulting from the vascular spasm caused by the convulsions.

Case History. A female, aged 52, entered this hospital with the complaint of severe abdominal pain. There was generalized boardlike rigidity of the abdomen and tenderness on palpation. The patient had first noticed abdominal pain 30 hours before entrance to the hospital. The respirations were rapid and shallow, the pulse very rapid, weak and irregular. The systolic blood pressure was 60, the temperature 104° F. An indirect blood transfusion was given, intravenous fluids and 4 gm. of sodium sulfapyridine in 500 cc. of distilled water. The Levine tube with continuous suction was used. The patient expired 6½ hours after admission. Five days before entering the hospital, she received an injection of metrazol for involutional melancholia which resulted in typical convulsive seizures. One or two injections had been given previously. There was no history or evidence of trauma to the epigastric region.

Autopsy findings (abdominal incision only): The abdomen contained considerable gas; the peritoneum was dull, purple-gray mottled with fibrinous deposits and contained about 500 cc. of dark brown fluid. There was a punched-out perforation (7 by 6 mm.) in the anterior surface of the first portion of the duodenum 1 cm. from the pylorus. Its edges were soft and brown stomach contents could be expressed. The anterior surface of the stomach was covered with a fibrinous exudate. The lesser peritoneal sac contained no fluid and the surfaces were smooth. The loops of small intestine were heavy and contained large amounts of fluid. In several areas, the serosa was covered by a fibrinous exudate.

Microscopic examination: The walls of the duodenal ulcer showed necrotic tissue along the edges of the ulcer, beneath which were small infiltrations of lymphocytes, mononuclear cells and neutrophils. No evidence of fibrosis was found (Van Gieson). The anatomic diagnosis was generalized fibrinopurulent peritonitis, acute perforated duodenal ulcer and fatty degeneration of the liver.

Discussion. The punched-out nature of the defect in the anterior wall of the duodenum, the lack of hemorrhage in the wall adjacent to the perforation, the absence of any evidence of direct injury to the epigastrium together with the absence of a history of a chronic

ulcer serves to eliminate a traumatic origin of the ulcer, except for the possibility of excessive flexion during the convulsion as a possible contributing factor. The thickened appearance of the anterior wall of the proximal 3 cm. of the duodenum was found to be due chiefly to large groups of Brunner's glands in the submucosa (Fig. 1). Comparison of the anterior wall of the first portion in the normal duodenums of other autopsies, together with the extensive studies of Feyrter[6] and Robertson[16] on the pathology of Brunner's glands, leads to the conclusion that the suspected hyperplasia came within the upper limits of normal. The possibility of abnormal pressure on the duodenal mucosa was considered because of the earlier contention of Scagliosi[17] that duodenal ulcers may be caused by hyperplasia of Brunner's glands with subsequent pressure on the mucosa. However, this theory has not been substantiated by later investigators.

FIG. 1.—A sagittal view taken through the first part of the duodenum at a point 2 mm. from the right edge of the perforating ulcer of the anterior wall.

An attempt to explain the way in which metrazol could produce peptic ulceration necessitates consideration of vascular and neurogenic factors. Experimental work leading to the production of peptic ulcers strongly suggests that the main underlying factor is a local circulatory disturbance. Boles, Riggs and Griffiths[3] and Boles and Riggs[2] concluded that focal gastric ulcers were due to focal manifestations of a generalized circulatory insufficiency. Also the work of Reeves,[13] Wilkie[21] and the more recent investigations of Wilmer[22] on the blood supply of the first part of the duodenum give some anatomic basis for explaining the localization of ulcer lesions in the pyloric region of the gastro-intestinal tract. In the studies of Berg[1] and Nedzel,[12] on the experimental production of peptic

ulcers by means of pitressin, anoxemia is produced not only by direct action on the small blood-vessels but by a compression of the larger blood-vessels by muscular contractions of the walls of the stomach and duodenum.

The action of large doses of metrazol on the vascular system according to Haury and Gruber[8] is similar to the effect of adrenalin. They concluded from experimental studies that two effects on the vascular system may be obtained, depending on the size of the dose of metrazol: one a central action causing splanchnic constriction, and the other a peripheral effect causing splanchnic dilatation. Messinger and Moros[10] have noted that patients with hypersensitivity of the sympathetic nervous system may exhibit symptoms of hyperadrenalinemia.

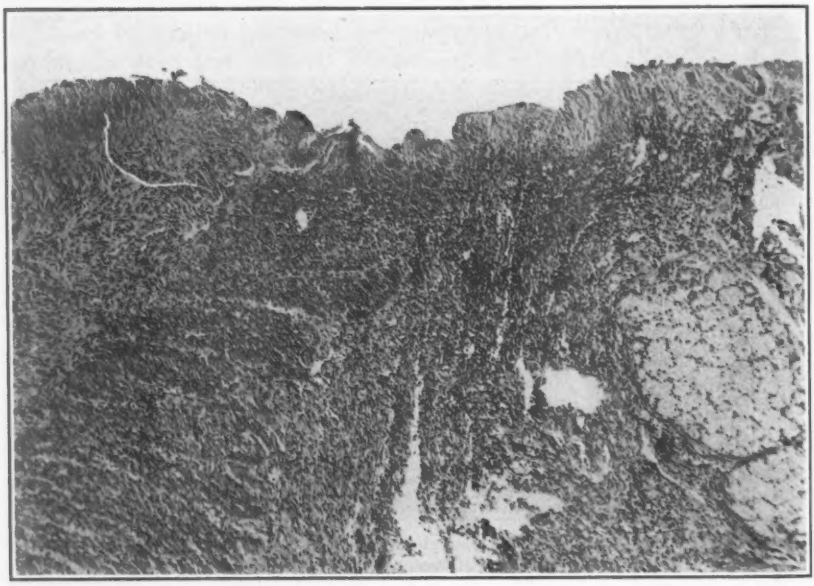

FIG. 2.—Section through the wall of the perforation, showing the distinct muscular coats and the narrow necrotic zone lining the defect. No fibrosis of a chronic ulcer is present. (× 40.)

Certain neurogenic impulses can have profound effects on the terminal vascular system of the gastro-intestinal tract (Boles and Riggs[2]). This may appear after injury or stimulation of the brain, particularly of the hypothalamic regions. The stimulation of the vegetative centers may cause peripheral stasis or vasoconstriction through an imbalance of the sympathetic and parasympathetic nervous systems. This concept is essentially that used by Cushing[4] to explain the pathogenesis of peptic ulcer. He concluded that abnormal vagal impulses could lead to hypersecretion, hyperchlorhydria, hypermotility and hypertonicity particularly in the pyloric region,

causing spasmodic contractions of the musculature and possibly spasms of the terminal blood-vessels, leading to a devitalized area which may be then acted upon by the gastric juice.

Summary. The occurrence of an acute, perforated duodenal ulcer following soon after metrazol therapy is reported. The theories considering the possible relationship of the effect of metrazol on the nervous system and a "neurogenic" ulcer are briefly discussed. In view of the rarity of this type of complication following metrazol injections, however, the possibility of coincidence must be considered.

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A DIET CALCULATOR FOR SIMPLIFYING DIET PRESCRIPTION IN DIABETES MELLITUS.

By Theron G. Randolph, M.D.,
MILWAUKEE, WIS.

Many of the significant advances in the science of nutrition have not been applied in the treatment of disease. This discrepancy between principle and practice may be due in part to the fact that many physicians have not been trained adequately in practical dietetics and in part to the fact that the writing of diet prescriptions remains a time-consuming procedure. As a result, it is a common practice to use a few favorite stock diets instead of giving patients individual dietary attention. This criticism may be directed particularly toward the dietary management of diabetes mellitus or

other conditions in which it is desirable to regulate accurately the caloric value of the diet as well as the content of carbohydrate, protein and fat.

The Diet Calculator. In an attempt to simplify this problem the essential information used in the dietary treatment of diabetes mellitus has been assembled on a circular chart called a Diet Calculator.* By manipulating the movable parts of this instrument one may select the desired therapeutic diet to meet the needs of a particular case.

The device, as illustrated in Figure 1 consists of three concentric disks, the two outer disks form the front and back dial faces and rotate upon a slightly larger inner disk. One hundred diets are listed. The various details of a single diet may be read through the windows of the dial face as its pointer is directed toward a given sector on the periphery. Figure 1 illustrates the front view; the back view is similar except that the diets possess higher caloric values.

Use of Calculator. The number of calories required for a given patient may be determined by reference to the tables upon the face of the Calculator. After choosing the level of calories and selecting that specific division on the periphery of the Calculator, one then selects a diet within that range of calories by rotating the pointer of the dial face to the desired amount of available glucose† listed in the most peripheral window, or if preferred, to the content of carbohydrate, protein and fat named in the second window. The characteristics of the diet in terms of basic foods may then be read through the remaining windows, in which are listed the total food required for the day and the amounts of food for each of the three daily meals.

The following basic food groups are used: eggs, bacon, milk, 10% fruit or vegetable, bread, 20% cream, and butter. For convenience the principal source of protein is expressed in terms of eggs, other protein-containing foods which may be substituted for eggs are tabulated upon the back face of the instrument. The bulk of the diet may be regulated by substituting 5%, 15%, or 20% fruits and vegetables for amounts of 10% fruits and vegetables. The quantities of the various foods are such as to be readily convertible to measure if weighing of the diet by means of a gram scale is not desired. The classification of fruits and vegetables according to carbohydrate content in terms of 100 gm. portions with the equivalent in household measures is tabulated on the back dial face.

In these diets the morning meal contains $\frac{1}{5}$ and each of the two remaining meals $\frac{2}{5}$ of the total daily available glucose. By means of a simple adjustment as described on the front dial of the Calculator, it is possible to secure either an equal division of the available glucose among the three daily meals ($\frac{1}{3}-\frac{1}{3}-\frac{1}{3}$) or to allow for a bedtime feeding ($\frac{1}{5}-\frac{1}{3}-\frac{1}{3}-\frac{2}{15}$).

* Published by E. R. Squibb & Sons, 745 Fifth Avenue, New York, N. Y.

† The available glucose is derived from the metabolism of 100% of the carbohydrate, 50% of the protein and 5% of the fat. (Newburgh and MacKinnon, The Practice of Dietetics, New York, The Macmillan Company, 1934.)

The energy value of these prescriptions differs by units of 200 calories with a range from 800 to 2800 calories. The available glucose content of the individual diets varies by gradations of 15 gm., the range extending from 65 to 275 gm. This variation is shown graphically in Figure 2, in which the available glucose is plotted horizontally and the calories vertically. The various com-

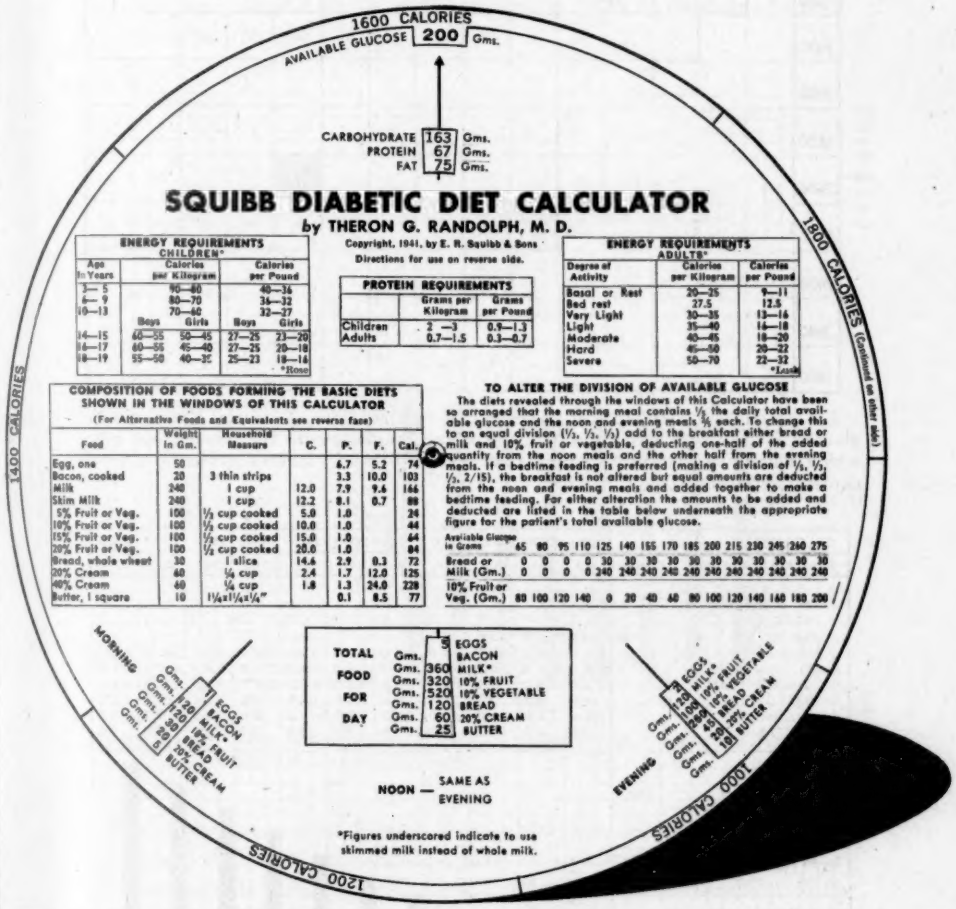
1600 CALORIES
AVAILABLE GLUCOSE 200 Gms.
CARBOHYDRATE 163 Gms.
PROTEIN 67 Gms.
FAT 75 Gms.
SQUIBB DIABETIC DIET CALCULATOR
by THERON G. RANDOLPH, M. D.
Copyright, 1941, by E. R. Squibb & Sons
Directions for use on reverse side.
ENERGY REQUIREMENTS CHILDREN*
ENERGY REQUIREMENTS ADULTS*
PROTEIN REQUIREMENTS
COMPOSITION OF FOODS FORMING THE BASIC DIETS SHOWN IN THE WINDOWS OF THIS CALCULATOR
(For Alternative Foods and Equivalents see reverse face)
TO ALTER THE DIVISION OF AVAILABLE GLUCOSE
The diets revealed through the windows of this Calculator have been so arranged that the morning meal contains 1/5 the daily total available glucose and the noon and evening meals 2/5 each. To change this to an equal division (1/3, 1/3, 1/3) add to the breakfast either bread or milk and 10% fruit or vegetable, deducting one-half of the added quantity from the noon meals and the other half from the evening meals. If a bedtime feeding is preferred (making a division of 1/5, 1/5, 1/5, 2/15), the breakfast is not altered but equal amounts are deducted from the noon and evening meals and added together to make a bedtime feeding. For either alteration the amounts to be added and deducted are listed in the table below underneath the appropriate figure for the patient's total available glucose.
1800 CALORIES (Continued on other side)
1400 CALORIES
1200 CALORIES
1000 CALORIES
MORNING
EVENING
NOON — SAME AS EVENING
TOTAL FOOD FOR DAY
5 EGGS
BACON
360 MILK*
320 10% FRUIT
520 10% VEGETABLE
120 BREAD
60 20% CREAM
25 BUTTER
*Figures underscored indicate to use skimmed milk instead of whole milk.

FIG. 1.—Front face of diet calculator. Note one window just above the largest lettering and three others in the lower part of the disc.

binations of these two factors comprising the 100 diets are represented by the crossed squares in the center of the diagram, each square representing a single diet. When these squares are viewed in a horizontal series, one should note that the diets of each level are characterized by having an identical caloric value but a varying content of available glucose. Figure 3 illustrates the composition of the diets containing 2000 calories as the available glucose increases

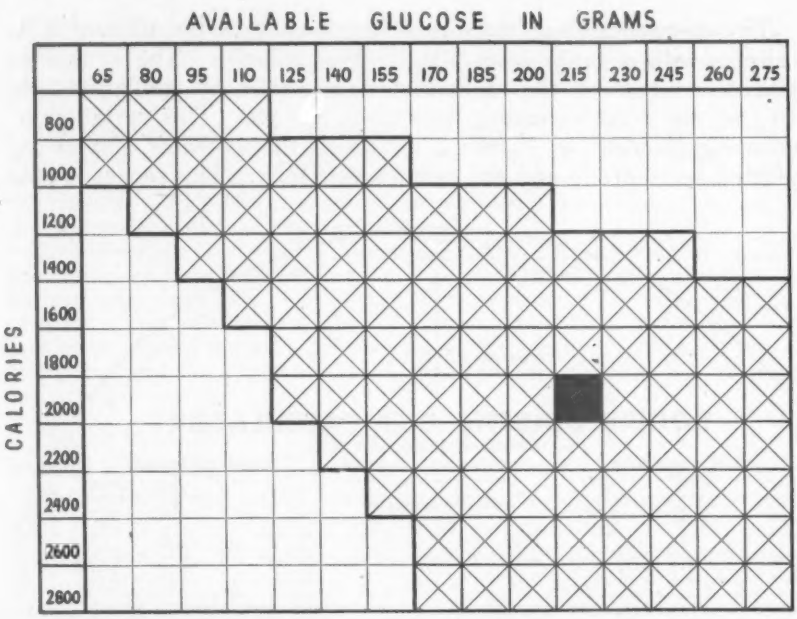

FIG. 2.—The crossed squares represent the combinations of calories and available glucose in the 100 related diets. The inked square designates the prescription from which successive isocaloric diets and successive diets of constant available glucose content were prepared.

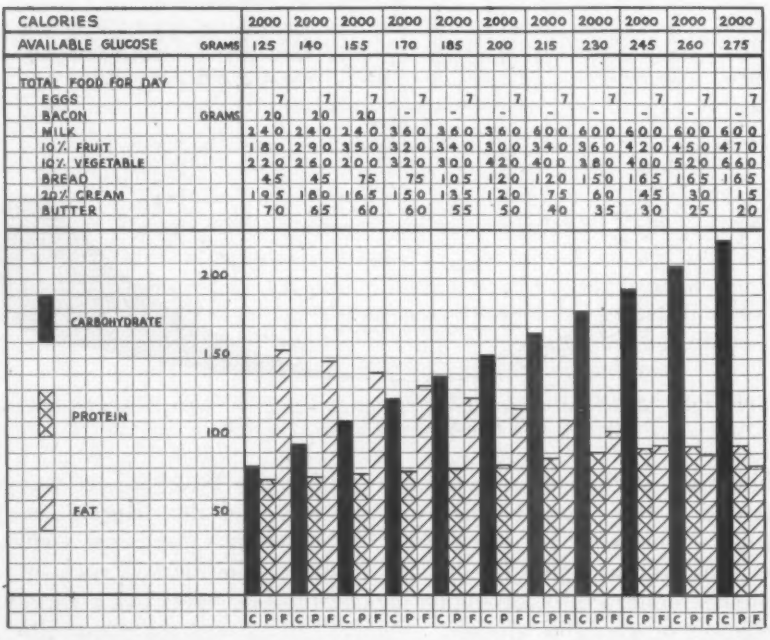

FIG. 3.—Composition in terms of food groups, carbohydrate, protein, and fat of the isocaloric diets of 2000 calories and a varying content of available glucose.

from 125 to 275 gm. In reading this sample series from left to right one should note the steplike increases in carbohydrate and the decreases in fat existing between the individual diets, also the graded variations in the constituent food groups. It is to be observed that the prescriptions toward the left of the series are of relatively low carbohydrate and high fat value, those toward the right of relatively high carbohydrate and low fat value, whereas the diets midway between these two extremes possess a ratio of carbohydrate to fat of approximately 1 to 1.

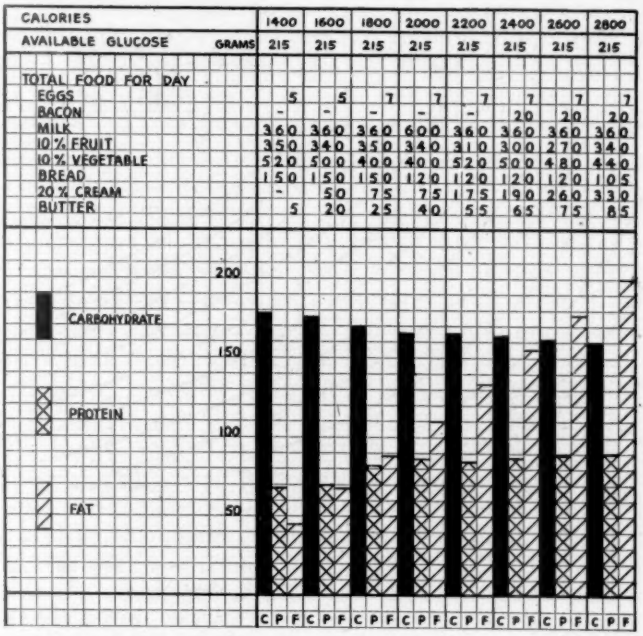

FIG. 4.—Composition in terms of food groups, carbohydrate, protein and fat of diets containing 215 gm. available glucose and a varying content of calories.

When the squares of Figure 1 are viewed in vertical columns, the individual diets have a constant level of available glucose but vary by units of 200 calories. Figure 4 illustrates the composition of the diets of a sample vertical series, namely those containing 215 gm. available glucose as the calories are carried through the range from 1400 to 2800. As in the previous example, one may observe the variations between the individual diets in terms of carbohydrate, protein, and fat as well as in the constituent food groups.

Mathematical Construction of Diets. The preparation of this series of 100 interrelated diets may now be explained. The diet of 2000 calories and 215 gm. available glucose (see inked square in Figure 2) served as the starting point. Other diets of 2000 calories

containing progressively less available glucose (*i. e.*, 200, 185, 170, etc. gm.) were constructed by making repeated subtractions in terms of foods rich in carbohydrates and repeated additions in terms of foods high in fat value. A formula was prepared listing the increments or decrements in terms of the basic food groups as well as the resulting change in the values of carbohydrate, protein and fat which occurred in a reduction of 15 gm. available glucose (*i. e.*, moving one square to the left in Figure 2). The successive isocaloric

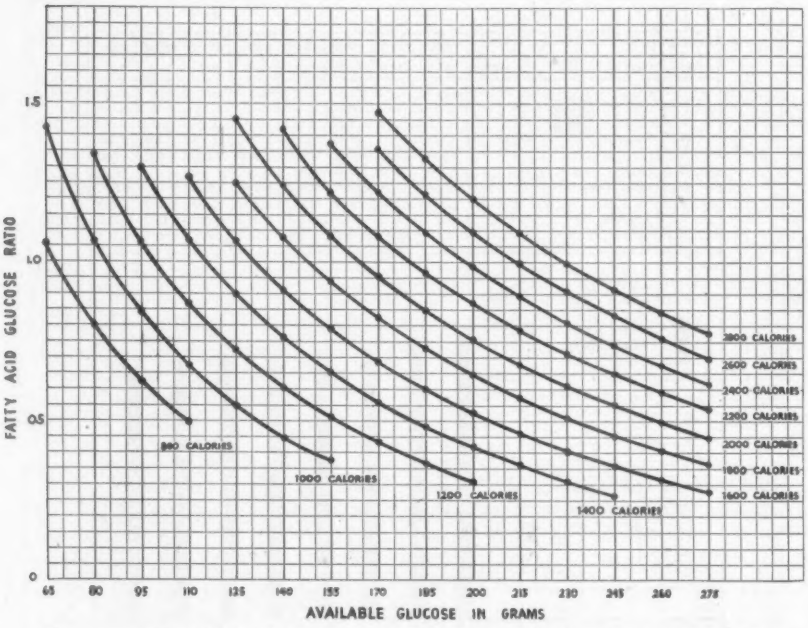

FIG. 5.—The fatty acid glucose ratios of the standard diets of the Calculator. Interesting from the mathematical standpoint is the fact that the individual points making up the curves of this figure may be on semicubical parabolas according to the equation:

$$\frac{\text{Fatty acid}}{\text{Glucose}} = \frac{1.155 \text{ calories} - 390}{(\text{Available glucose})^{3/2}}$$

(This equation was contributed by Dr. John Bugher.)

diets of decreasing available glucose content were prepared in the same manner. Conversely, the formula with opposite signs was used in constructing adjacent isocaloric diets of increasing available glucose content (*i. e.*, moving square by square to the right in Figure 2).

The successive diets in the vertical series of 215 gm. available glucose and varying calories (see Figure 2) were constructed in a similar mathematical fashion, again starting with the initial diet of 2000 calories and 215 gm. of available glucose (see inked space).

The same formula was not used in constructing each successive diet of an entire horizontal or vertical series. At intervals within each series the formula was changed in order to regulate the bulk of the diet and to keep the prescriptions well balanced.

The fatty acid glucose ratio of each diet is plotted in Figure 5. Connecting the plotted points for each group of isocaloric diets results in a series of arcs the curvature of which decreases as the caloric values increase. It will be noted that in no instance does the ratio exceed 1.5.

The use of this mathematical approach results in a series of 100 closely related therapeutic diets. The constant and gradual change occurring between individual isocaloric prescriptions is a significant feature. Under certain circumstances it is desirable to change a diabetic diet by small and repeated increments or decrements of carbohydrate. These prescriptions are constructed to allow for such manipulation with the least possible alteration in the diet's basic structure yet maintaining the calories at a constant level.

Accompanying the Calculator is a booklet of instructions which explains in detail how the instrument is used. Included in the booklet are substitution tables which may be used in case one wishes to convert the standard diet prescriptions of the Calculator to diets of higher protein content. There is also provision for the addition of milk to children's diets.

By reference to other tables the caloric or available glucose content of a given diet prescription may be increased or decreased. These tables are useful in cases where the standard diets of the Calculator have been altered in terms of the constituent basic foods. An alteration, such as the addition of milk to the diet of a child, may be retained as the energy value of the prescription is changed by units of 200 calories or the available glucose altered by 15 gm. In each case the resulting value of carbohydrate, protein and fat is tabulated.

No attempt is made to outline procedure in the dietary therapy of diabetes mellitus. This material is presented with the aim of supplying in a simple and usable form the essential dietary information applicable to the treatment of diabetes. Depending upon the needs of the particular patient or upon the point of view of the physician, one may select adequate diets of varying energy content relatively high or low in carbohydrate, protein or fat.

Summary. A Diet Calculator listing the details of 100 therapeutic diets and providing for alterations in these prescriptions to meet the requirements of individuals with diabetes mellitus is described.

The mathematical approach in constructing this series of interrelated diets is explained.

BOOK REVIEWS AND NOTICES

ALLERGY IN CLINICAL PRACTICE. By Staff-members of the Cleveland Clinic. Under the Direction of RUSSELL L. HADEN, M.D., F.A.C.P., Chief of the Medical Division; Edited by J. WARRICK THOMAS, M.D., F.A.C.P., Chief of the Section on Allergy. Pp. 354; 92 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, $5.00.

THE concept responsible for this volume, to write for the general practitioner a text on allergy with a minimum of theory and technique and with a maximum of the practical as set forth in numerous case reports, is most laudable, but the result leaves much to be desired. After a very inadequate introductory chapter on the "Approach to the Problem of an Allergic Patient" (in which pruritis is referred to as a lesion), there follow chapters on asthma, hay fever, perennial nasal allergy, allergic bronchitis, bronchiectasis, the cutaneous allergies, gastro-intestinal allergy, the ocular manifestations of allergy, migraine, endocrine considerations in the allergic patient, uncommon manifestations of allergy. Only the chapters on the cutaneous manifestations of allergy deserve high praise. By contrast the chapter on asthma is sketchy and incomplete. The discussion of gastro-intestinal allergy is very inadequate. The chapter on endocrine considerations is not pertinent and only beclouds the issue. Urinary tract allergy is dismissed with 3 case reports. Very few of even the most enthusiastic allergists would subscribe to the view that *all* hay fever patients should be thoroughly tested to foods as well as inhalants. The book is not recommended.

R. K.

L'ÉTAT PRÉ-CANCÉREUX. Signification Biologique. By J. M. MONTPELLIER, Professeur of Pathological Anatomy, School of Medicine, University of Algiers, North Africa. Pp. 268; with numerous plates. Algiers: Jules Carbonel, 1941. Price about $2.00 (52 francs French).

THIS book, having as its purpose the study of the biologic concept of the precancerous state and the question of suitable cancer prophylaxis, contains much interesting information. Up to the present day the concept of the precancerous state has always been a subject for much controversy. While many cancerologists are of the opinion that the precancerous state is bound to manifest itself as cancer sooner or later, others regard it as one which may or may not manifest a tumor later on. According to still other scientists, a lesion is either cancerous or non-cancerous; aside from the biologic, clinical, and histologic standpoints, it is impossible to diagnose the "precancerous state."

The author, in spite of the complexity of the problem, attacks it very courageously, and gives us a very interesting and instructive book.

Book 1 deals with the precancerous state in humans. Its characteristics are a local process accompanied by a general process. To quote the author: "When we observe the initial stages of cancer, we notice a phenomenon which is constant—the malignant tumor does not appear haphazardly, at any part of the body, or suddenly even. Before the appearance of a cancer, there are always local premonitory signs. This premonitory local state is always present in human and animal cancer cases before the appearance of the tumor. Thus, there is no cancer without a previous local precancerous state." In many cases, these precancerous states may regress and disappear entirely before a cancer has appeared. This phenomenon is noticed both during the development of a spontaneous cancer and during an experi-

mentally induced cancer. The fact that a precancerous state may disappear or develop into cancer itself in no way affects the biologic significance and importance of the precancerous problem.

Histologically, a precancerous state is a process of cellular and tissue change ("remaniement"), during which regressive and progressive phenomena are noticed. But what is striking in this connection is not so much the regression and the progression of tissue—the static state—but the dynamic state of the tissue. That is to say, an exaggerated and disorderly generative cell-action.

The author goes on to describe these local precancerous states—mild tumors, embryonic and organic malformations, scars, chronic irritations, intoxications and so on.

This book also deals with the precancerous states in comparative pathology, such as spontaneous and induced cancer in animals and plants. From the biologic point of view, all cancers, human or animal, induced or spontaneous, are always preceded by initial local lesions which are precancerous.

Book 2 deals with the biologic significance of the precancerous state. Precancerous states are of many different kinds and often give the clue to the cancer itself. No cancer appears without having first been "announced" by a local precancerous state. In this part of his book, the author gives clinical, histologic and chemical descriptions of these various states.

This part of the book also treats of the "cancerous terrain." The author concludes that it is logical to accept the existence of a general precancerous state, in certain patients. This general "precancerosis" is regarded as a specific receptivity of the body to cancerization. Thus, local conditions being the same in both cases, the patient with no receptivity does not develop cancer, while the other patient (who is receptive) does. But we must admit that on such speculative ground, investigation must be controlled with a special caution. For this idea of the precancerous state is important in all present-day practical cancerology. That is why this book should be read, not only by the cancerologist, but by physicians generally.

Book 3 deals especially with cancer prophylaxis. The author formulates numerous methods which may be used to: *a*, combat the transformation of a precancerous state into cancer itself; *b*, eliminate the formation of a precancerous state. These methods include hygienic measures designed to protect the skin, the mucosa, and the internal organs against local precancerous states. By general hygiene, such as special diet, the elimination of certain dangerous cancerogenic substances, such as drugs, certain foodstuffs, arsenic, folliculin, etc., the formation of cancer can be avoided. A special hygiene for the nervous system must also be used in cancer prophylaxis. As soon as a slight alkalosis of the blood, or a surplus of cholesterol, is observed, measures must be taken to eliminate these conditions. Chronic infection and intoxication must be avoided.

The author also deals with the question of hormones and precancer, professional diseases, and the counter-measures to be employed, the social and medical services which should function in each country, and a special cancerologic training for the medical body.

This is a book which should find a place in every doctor's library.

J. S.

SINUS. By RUSSELL CLARK GROVE, M.D., Assistant Otolaryngologist, and Chief Otolaryngologist of Allergy Clinic, Roosevelt Hospital. Pp. 188; 16 illustrations. New York: Alfred A. Knopf, 1941. Price, $2.00.

WRITTEN for the layman, who unfortunately has as a rule a large store of misinformation on "sinus," this book presents a discussion of the anatomy and physiology of the paranasal sinuses, the causes and types of sinus

disease, the symptoms, diagnosis and complications of sinusitis, and the rationale of the medical and surgical treatment of these conditions. While in places the going may be a bit heavy, the intelligent layman will find the book both useful and instructive. R. K.

THE ECLIPSE OF A MIND. (Autobiography with a Preface by an "Anonymous Attending Physician.") By ALONZO GRAVES. Pp. 722. New York: The Medical Journal Press.

THIS is a hard book to review. It is unique in presenting a patient's account of manic-depressive attacks side by side with very good hospital records. The patient's sex life is given in voluminous detail. The chapter on heredity and environment is admirable as is the author's detached and scientific discussion of the "bored and kindly custodial treatment of human livestock." His discussion of the origin of mania in himself is full of good suggestions and is well thought out. Not the least surprising thing in this unusual book is the author's disappearance into Russia.

It will be of great interest to psychiatrists and also to workers in fields related to psychiatry. Because of the unusual character of this book, attitudes toward it will depend much on the background of the reader.

E. B.

SYMPTOM DIAGNOSIS. Regional and General. By WALLACE MASON YATER, A.B., M.D., M.S. (in Med.), F.A.C.P., Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine; Physician in Chief, Georgetown University Hospital and Gallinger Municipal Hospital, Washington, D.C., Formerly Fellow in Medicine, The Mayo Foundation. (Originally written by the Late WILFRED M. BARTON, A.M., M.D., F.A.C.P., and WALLACE M. YATER, A.B., M.D., M.S., F.A.C.P.) Fourth edition. Pp. 900. New York: D. Appleton-Century Company, 1942.

A USEFUL and convenient book for quick reference and help in diagnosis. It is concise, yet adequate. The material is well arranged and there are numerous classifying tables. The work, which justly merits its fourth edition, is highly recommended. R. K.

THE MODERN TREATMENT OF SYPHILIS. By JOSEPH EARLE MOORE, M.D., with the collaboration of J. E. KEMP, M.D., HARRY EAGLE, M.D., PAUL PADGET, M.D., MARY STEWART GOODWIN, M.D. Pp. 674. Second edition. Springfield, Ill.: Charles C Thomas, 1941. Price, $7.00.

COMING as it does from an originator of and spokesman for many of the most significant contributions, clinical and experimental to the syphilology of today, this new edition must be read by every serious student of medicine in one or another chapter of its many-sided presentations. It achieves with success the compromise between the encyclopedic authority and the practical utility of the desk volume. Part of this excellent effect is secured by hewing close to the line of the major contributions of the Johns Hopkins group, which are of a range and depth sufficient to reflect and voice the entire field. Certain of the chapters, as on syphilis of the eye and of the nervous system, are monographs embodying unrivaled experience, and will be repeatedly referred to by clinicians in one or another "tight spot." Similarly there are modestly tucked away in other presentations (as in early syphilis) gems of original contribution whose luster can best be appreciated by the expert who has watched the progress of thought in this field

over a period of years, and knows that they represent pivotal points that determined the course of future thought and procedure.

The defects of the work, as the reviewers see them, are of much less significance, and are perhaps inevitable by-products of a group mode of approach, carried to its conclusion. The work was directed by one of the most brilliant, incisive, positive, and critical minds in the field. It is to be expected and indeed hoped that it will contain *obiter dicta*, *ipse dixit*, and *ex cathedra* statements, not always on adequately examined premises. It does. It requires no use of the vulgar device of illustration (p. 175) to make a sensitive reader read page after page of flat print indulging now and again in the excellent exercise of grinding his teeth and bounding from his chair. All this is for the best, and stimulating both for the cerebral vertex and the suprarenal medulla. If the authorship can carry the pace, the reader should, and he will; but not without creaks over the corduroy. There is an apparent disposition to cite outside views for the purpose of demolishing them, sometimes with needless acerbity, or to interpose the negative on insufficient or admittedly no evidence. There are outright misstatements of others' views quoted from obsolete citation (*cf.* the resistance building *vs.* the spirocheticidal mechanism in bismuth action), apparently to act as foils for the authors' more recent contributions. The strong group flavor sometimes becomes overwhelming like the otherwise laudable and delectable odor of allyl sulphide which in sufficient concentration can provoke tears. The best description of the ninth day erythema (stated to be a neglected topic, though adequately described in at least two American and many European sources) is by a Johns Hopkins author not yet in print at the time of this book's citation. This disposition to beat the starting gun confers merely an added piquancy. But the bibliography thus drawn must be emphatically described as inadequate and a bit deceptive—especially since statements are not tagged to their bibliographic citations in many cases, so that a reader cannot check or judge strictures and evaluations from their context. There are occasional indications, as in the interpretations of non-specific effects of treatment, that the writing of a text on syphilis from the viewpoint and equipment of an internist may have its shortcomings, like writing from that of a dermatologist or other -ologist.

But all this is minor animadversion and really praises the work as human, as well as stimulative, informative, authoritative. The best and the most final comment on Moore on Treatment is this: when the expert of the future and the historian of the past prepare to write on the management of syphilis they will have to read Moore, word by word, or miss the essence of the subject. J. S. N. I.

TREATMENT OF THE PATIENT PAST FIFTY. By ERNEST P. BOAS, M.D., Associate Physician, Mount Sinai Hospital, New York City; Chairman, Committee on Chronic Illness, Welfare Council of New York City; Assistant Clinical Professor of Medicine, Columbia University. Pp. 324; 19 illustrations. Chicago: The Year Book Publishers, Inc., 1941. Price, $4.00.

THE past 50 years have witnessed a steady increase in the proportion which the elderly comprise in our population. It has been estimated that, if present trends continue, by 1980 nearly 15% of the American people will be past the age of 65. The present text deals with problems of prophylaxis, diagnosis and treatment of disease in those past 50. From the standpoint of the various organic diseases, which are systematically discussed, the material is well handled. More might have been said about functional disorders and the psychic and medico-social problems so common among those of advanced years. Especially the young physician will find much that is helpful in this book. R. K.

ROENTGEN TREATMENT OF INFECTIONS. By JAMES F. KELLY, M.D., F.A.C.R., Professor and Director of the Department of Radiology, Creighton University School of Medicine; Attending Radiologist, Creighton Memorial, St. Joseph's, St. Catherine's and Douglas County Hospitals, Omaha, and Mercy Hospital, Council Bluffs: With the Collaboration of D. ARNOLD DOWELL, M.D., Assistant Professor of Radiology, Creighton University School of Medicine, etc. Pp. 432; 122 illustrations. Chicago: The Year Book Publishers, Inc., 1942. Price, $6.00.

THIS is a carefully prepared textbook with a good index and extensive bibliography. It includes a review of all cases of gas gangrene, treated by Roentgen ray, in this country, that have come to the authors' attention.

The first two chapters of the book contain a brief discussion of Roentgen ray physics and general considerations of Roentgen ray therapy in infections with a history of the development of the mobile therapy machine. The main portion of the book deals with the Roentgen ray treatment of gas gangrene and acute spreading peritonitis. The authors are pioneers in this field and have carefully analyzed their experiences in the management of these serious infections over more than 10 years. They produce convincing proof that in their hands early Roentgen ray treatment for gas gangrene and acute peritonitis is the method of choice. In both gas gangrene and peritonitis, Roentgen ray treatment should be given in small doses every 8 to 12 hours for the first few days until the toxemia of the disease has disappeared. Under this régime, early amputation and the use of serum is superfluous and may actually do harm. The authors believe that the use of sulfanilamide with Roentgen ray treatment is contraindicated, and that Roentgen ray alone has proven more beneficial than sulfanilamide alone, in the rapidly spreading anaërobic infections.

The last three chapters deal with the Roentgen ray treatment of superficial infections, parotitis, and pneumonia. In these conditions, also, the writers believe that Roentgen ray therapy may be a life-saving procedure.

There is no doubt that the authors have made a very important contribution to the practice of medicine through years of patient investigation in the field of treatment of infection, particularly gas gangrene, by Roentgen rays. It must be said, however, that the conversational style of this book and its frequent unnecessary repetition detract somewhat from the valuable material presented. All the essential points could be covered in a much smaller number of pages, and the result would be made easier to read.

R. B.

SURGERY OF THE AMBULATORY PATIENT. By L. KRAEER FERGUSON, A.B., M.D., F.A.C.S., Lieut.-Commander, Medical Corps, United States Naval Reserve; Assistant Professor of Surgery, University of Pennsylvania; Assistant Surgeon, Hospital of the University of Pennsylvania; Surgeon, Philadelphia General Hospital and Doctors Hospital; Consulting Surgeon, Frankford Hospital; Chief of the Surgical Out-patient Department, Hospital of the University of Pennsylvania; Chief of the Proctologic Clinic, Hospital of the University of Pennsylvania and Philadelphia General Hospital. With a Section on Fractures by LOUIS KAPLAN, A.B., M.D., F.A.C.S., Associate in Surgery, University of Pennsylvania; Associate in Surgery, Mt. Sinai Hospital; in charge of the fracture division of the Surgical Out-patient Department, Hospital of the University of Pennsylvania. Pp. 923, 645 illustrations. Philadelphia: J. B. Lippincott Company, 1942. Price, $10.50.

THE average surgeon is apt to overlook the fact that actually the greatest number of surgical lesions are the so-called minor ones, that is, they do not require hospitalization of the patient. These lesions are, as a rule, treated by the general practitioner or by the younger surgeon. They do, neverthe-

less, require skill and judgment in therapy for disfiguring and even disabling results may follow careless treatment.

Doctor Ferguson has had many years of experience as head of an active surgical out-patient department. This volume is the result of his thoughtful approach to the surgical problems he has had to meet. It is a comprehensive, clear exposition of the surgical therapy he has found to be most effective and it can be fully recommended to every industrial or general surgeon.

The only criticism that might be offered is that a number of procedures are included which in the hands of Doctor Ferguson, who is an experienced general surgeon, might be safely done in the ambulatory patient, for example, the excision of a thyroglossal sinus, but which should not be done by a less skillful surgeon under these circumstances. I believe in the next edition of this book it would be well to include a few words of caution after certain of the more extensive procedures.

The illustrations are clear and numerous and the book is well arranged and well printed. I. R.

THE LYMPHATIC SYSTEM: ITS PART IN REGULATING COMPOSITION AND VOLUME OF TISSUE FLUID. LANE MEDICAL LECTURES. By CECIL K. DRINKER, Professor of Physiology and Dean of the School of Public Health, Harvard University. Pp. 101; 29 illustrations. Stanford University Publications, University Series. Medical Sciences, Vol. IV, No. 2, Stanford University, California, Stanford University Press, 1942. Price; bound $2.25; in paper, $1.50.

THE author's Preface explaining why this shorter book so soon follows his longer one on the same subject, aptly likens the essay to "a cruise in a ship built of experiments and ideas." He here develops the reasons why mammals have a lymphatic system, and why it has slowly developed into an important physiological entity complementing the blood circulation. The student of this short book will inevitably profit by the stimulating presentation of the evolution and function of the lymphatic apparatus; he may be even more stimulated and benefited by the author's persistent emphasis, in his well known picturesque and vigorous style, on the dynamic point of view and on the need for ideas and on their harmfulness unless converted through experiment into fact.

The twenty-eighth series of Lane Medical Lectures will stand high among its distinguished predecessors. E. K.

THE ELECTRON MICROSCOPE. By E. F. BURTON, Head of the Department of Physics and Director of the McLennan Laboratory, University of Toronto, and W. H. KOHL, Development Engineer, Rogers Radio Tubes Limited, Toronto. Pp. 233; 110 illustrations. New York: Reinhold Publishing Corporation, 1942. Price, $3.85.

KNOWLEDGE of form and structure has regularly and almost necessarily preceded knowledge of function—first knowledge of what might be seen with the naked eye, then of greater detail as supplemented by the magnifying powers of the microscope and telescope. It was not until a century ago that technical improvement of the compound microscope, especially with good achromatic lenses, permitted the accurate knowledge of plant and animal tissues in health and disease that revolutionized the biological sciences. In simple but accurate language, the authors explain the physical reasons for the limitations of the resolving and magnifying powers of the ordinary light microscope and of the slightly more powerful, "ultramicroscope." Thus the highest practical magnifications, 1800 to 2500, were capable of revealing the smallest bacteria, but not the filtrable viruses, even the largest molecules and so on.

DeBroglie's development of the theory of the dual nature of the electron (1923) opened the way to a new field of study, Electron Optics, and this in turn to the production of Electron microscopes, both electrostatic and magnetic, that permit of useful magnifications 20 to 50 times greater than had been previously possible. Already, in the medical field, for instance, it has become possible to photograph the viruses (Cp. on page 218, smallpox viruses, x113,400). Important new discoveries are being announced so rapidly that Koch's early days of bacteriology are recalled when it was necessary merely to shake the tree and new bacteria fell like ripe apples.

Such is the great story told by this little book, for the most part in simple language, together with the necessary underlying physics. The future usefulness of the method for many diverse fields of scientific investigations is indeed hard to exaggerate. Let us hope that the good start made on this Continent toward its practical applications may continue in spite of world conditions and even be a source of practical help to the United Nations in their vital struggle.

Those who know this field better than I tell me that this is a sound, reliable, well written book that fills an immediate need. One is surprised, however, at the kind of paper and screen used for the illustration of such difficult and highly magnified material. E. K.

MODERN BREAD FROM THE VIEWPOINT OF NUTRITION. By HENRY C. SHERMAN and CONSTANCE S. PEARSON, Columbia University. Pp. 118. New York: The Macmillan Company, 1942. Price, $1.75.

MODERN bread is a scientific attainment. Many advances in the growing of better wheat, in the milling of flour, improving its keeping qualities, and so on, have been made. But while the fine white bread of today retains its energy value and is more palatable and more generally digestible than the coarse dark bread of earlier times, it has suffered the loss of certain of its most valuable proteins, minerals and vitamins. The problem of the nutritionist is to suggest ways for the enrichment of flour or of bread so as to restore these lost constituents.

This book, from one of our leading laboratories of nutrition, has reviewed the whole question, and indicates the many possible ways by which a bread may be produced that, while furnishing as high as 50% of the total calories, will at the same time provide adequate calcium, iron, essential amino acids, and at least two of the important B vitamins, thiamin and nicotinic acid.

An excellent bibliography is appended, and a subject index. E. W.

LANGUAGE IN ACTION. A Guide to Accurate Thinking. By S. I. HAYAKAWA, Assistant Professor of English, Illinois Institute of Technology. Pp. 245. New York: Harcourt, Brace & Co., 1941. Price, $2.00.

AND

SCIENCE AND SANITY. An Introduction to Non-Aristotelian Systems and General Semantics. By ALFRED KORZYBSKI, Author, *Manhood of Humanity*, Director, Institute of General Semantics. Pp. 798. Illustrated. Second Edition. Chicago: The International Non-Aristotelian Library Publishing Company, 1941. Price, $6.00.

To the many of us who have only in the past year or so become aware of Semantics as an important mental discipline it will be a surprise to learn that the first edition of "Science and Sanity," the key to the scriptures of this discipline, appeared in 1933; that there have been two International Congresses on the subject, 1935 and 1941; and that an Institute of General

Semantics has flourished in Chicago for the past 4 years. From the 34 page booklet of application and criticisms that accompanies Korzybski's second edition we further learn that many really eminent thinkers—philosophers, mathematicians, biologists, physicians, psychiatrists, lawyers, educators, industrialists—warmly endorse the fundamental importance of the concept for all branches of human thought.

Obviously it behooves us to know more about this. On page 19, we learn that the term "semantic" is derived from the Greek *semantikos* (significant) and was introduced into literature by Michel Bréal in his "Essai de Semantique." Bréal was a French philologist (b. 1832) whose essay (1897) was concerned with the term in relations to *sema* (a sign or symbol, as in semaphore). When one seeks for further definitions, however, one finds that the author, a Polish Count, mathematician, and engineer, plunges quickly into higher mathematics, non-elementalistic structures, relativity, infinity, non-Aristotelian and "extensional" (*vs.* "intensional") concepts, and similar abstruse abstractions. Stimulus to persevere in this heavy going is not found by the physician in such statements as "Disturbances of the semantic reactions in connection with faulty education and ignorance must be considered . . . . as sub-microscopic colloidal lesions." Nor is confidence engendered by the incompleteness of many of the references gathered mostly toward the end of the book.

One turns, therefore, with relief to Hayakawa's "Language in Action," an avowed attempt to interpret and popularize this new science of symbolism and especially to evaluate the meaning of words and to illustrate the influence of language on thought. Every thoughtful student or teacher of a subject who attempts to be accurate in thought and expression, soon comes to realize how many unnecessary misconceptions and misunderstandings obstruct progress through the use of ambiguous or misleading words or through substituting the abstract word for the concrete reality, the theory for the fact. These he will find adequately and entertainingly explained in the smaller book, together with other semantic pitfalls, such as the "loaded" ("snarl" or "purr") word, the "one-word-one-meaning" fallacy, the "two-valued orientation" (*e. g.*, that a question can have only two sides, as in "Have you stopped beating your wife?"), affective connotations and communications, dictionary limitations, and so on. If you are really concerned in making yourself understood by the other fellow and in understanding what he means rather than merely what he says, this book will surely help you, and it will, in passing, give you a much more satisfying attitude toward language as language. What a different world it would be if in daily conversation, in the public press, and in learned assemblies, one could always understand what the other was trying to convey! And in a crazy world, groping about for a lost *modus vivendi*, would not an adequate knowledge of Semantics be an important factor in producing a workable peace?

We strongly recommend this little book, written by an American citizen who for many years has taught in the Illinois institution, and a few readers; we believe, will find even greater profit in following the advice of the author of "Science and Sanity" that his book "should be read at least twice and preferably oftener."

E. K.

PEDIATRIC GYNECOLOGY. By GOODRICH C. SCHAUFFLER, A.B., M.D., Assistant Clinical Professor of Obstetrics and Gynecology, University of Oregon Medical School. Pp. 384; 66 illustrations. Chicago: The Year Book Publishers, 1942. Price, $5.00.

A TEXTBOOK dealing with pelvic diseases in children and adolescent girls is a welcome addition to the more general texts in this field. In his small volume the author opens with a discussion of the psychologic management

of the patient. He outlines the various methods of investigation of the pelvic diseases of children, describes their treatment, and includes chapters on urologic conditions and diseases of the rectum. A final chapter deals with the medicolegal aspects of rape and allied subjects.

The author takes a sensible view of the various remedies which have been suggested in the field of the endocrine therapy. All of his subjects are well covered. Few references are given and these appear as footnotes. A more extensive bibliography and one condensed at the end of the volume, which would include full titles, would enhance the value of the book.

The publishers have made an attractive volume; the print is large and easily read. The 66 illustrations are well chosen and clear. The author is to be congratulated upon giving due credit to those who assisted him in the preparation of certain chapters—a courtesy frequently overlooked by authors. The Reviewer recommends the volume to everyone who is practising general medicine. D. M.

THE HISTORY AND EVOLUTION OF SURGICAL INSTRUMENTS. By DR. C. J. S. THOMPSON (with a foreword by DR. CHAUNCEY D. LEAKE). Pp. 106; 115 illustrations. New York: Schuman's, 1942. Price, $8.50.

THE author is well known to readers of English medical history through his numerous entertaining and valuable works on various phases of the physician's and the apothecary's art. As Curator of the Royal College of Surgeons in Lincoln's Inn Fields, he fortunately had recently completed the present study, based largely on the collection in that Museum, before it was wiped out by Nazi vandalism. It is fortunate that we have at least this valuable substitute for the destroyed collection and its descriptions. Scalpels, saws, trephines, specula, forceps, lancets, tourniquets, trocars, operating tables—these are the kinds of instruments traced by Dr. Thompson from Egyptian and Grecian down to modern times. Excellent and necessary as are the many illustrations, one almost begrudges the space that they take to the exclusion of further information from this well-informed writer.

The book is unusually well-prepared and should be a valued possession of many more than surgeons and medical historians. E. K.

RABIES. By LESLIE T. WEBSTER, M.D., The Rockefeller Institute for Medical Research, New York. Pp. 168, 2 illustrations, 22 tables. New York: The Macmillan Company, 1942. Price, $1.75.

IT is certain that control of communicable diseases demands enlightened community effort based upon complete understanding of responsibility. It is equally certain that ignorance combined with emotional factors have prevented the eradication of rabies. But with this book available there can be no excuse for ignorance on the part of dog-owners, veterinarians, public health officers or physicians. In it the author has presented briefly and concisely the available facts necessary for complete understanding of rabies, its diagnosis and control. The book is divided into three parts: 1, The diagnosis of rabies; 2, the prevention of rabies; and, 3, "Appendices," in which are quoted statutes on the disposal of rabid dogs, licensing dogs and disposal of unowned dogs, disposal of vicious dogs, and confining animals to prevent spread of rabies. In addition, tables on the immunizing potency of antirabies vaccines are included, and rabies antibodies and their relation to immunity are discussed briefly. There is an adequate bibliography and an index. Throughout the book "what to do and how to do it," when rabies is suspected in a community or when man or animals have been bitten by rabid dogs, is emphasized. The book may be recommended without reservation. The author is to be congratulated. H. R.

NEW BOOKS.

Solving School Health Problems—The Astoria Demonstration Study. By DOROTHY B. NYSWANDER, PH.D. The Commonwealth Fund, Publishers, New York: 1942. Pp. 377; several tables. Price, $2.00.

A Short History of Nautical Medicine. By LOUIS H. RODDIS, M.D., Captain, Medical Corps, U. S. A. Published by Paul B. Hoeber, Inc., New York: 1942. Pp. 359; illustrations, 12. Price, $3.00.

Acute Injuries of the Head. By G. F. ROWBOTHAM, B.Sc., F.R.C.S. Published by Williams & Wilkins Co., Baltimore: 1942. Pp. 288; illustrations, 124. Price, $6.00.

Arthrodesis. By G. F. ROWBOTHAM, B.Sc., F.R.C.S. Published by Williams & Wilkins Co., Baltimore: 1942. Pp. 132; figures, 144. Price, $7.50.

Gastro-intestinal Diseases. By various contributors to the Medical Clinics of North America. Published by Saunders. May, 1942. Vol. 26, No. 3. Pp. 350; illustrations, 21.

Memorable Days in Medicine. A Calendar of Biology and Medicine. By PAUL F. CLARK, and ALICE SCHIEDT CLARK, Department of Bacteriology of the University of Wisconsin Medical School. University of Wisconsin Press, Madison. Pp. 305, Frontispiece, 38 illustrations. First edition, 1942. Price, $2.00.

Better than a day by day Medical History Calendar, this booklet presents for every day in the year one or more anniversaries of memorable events, with anything from a line to a page describing each event. It was published in briefer form in *Medical Life* in 1936–1937.

Doctor Bard of Hyde Park. By J. BRETT LANGSTAFF. E. P. Dutton & Co., New York: 1942. Pp. 365; illustrations, 12. Price, $3.75.

Annual Review of Physiology. J. M. LUCK, Editor. Published by American Physiological Society, Inc. Pp. 709; figures, 2. First edition, 1942. Price, $5.00.

Female Sex Hormone Therapy; The Follicular Hormone, Part I—(eighth edition), Part II, the Corpus Luteum Hormone (first edition). *Male Sex Hormone: Therapy:* A clinical guide (first edition). Set of 3 books issued by Shering Corp., Medical Research Division, Bloomfield, N. J.: 1941.

Medical Manual of Chemical Warfare. Reprinted by Permission of The Controller of His Britannic Majesty's Stationery Office. Revised edition: 1942. Chemical Publishing Co., Inc., Brooklyn, N. Y. Pp. 121; plates, 10. Price, $2.50.

The Electrocardiogram and X-ray Configuration of the Heart. By ARTHUR M. MASTER, B.S., M.D., F.A.C.P. Lea & Febiger, Philadelphia: Second edition, 1942. Pp. 404; figures, 108; illustrations, 163. Price, $7.50.

Text-book of Pathology. By SIR ROBERT MUIR, M.A., M.D., Sc.D., LL.D., F.R.S. The Williams & Wilkins Co., Baltimore: Fifth edition, 1942. Pp. 991; figures, 599. Price, $10.00.

Management of the Sick Infant and Child. By LANGLEY PORTER, B.S., M.D., M.R.C.S. (England), L.R.C.P. (London), Dean Emeritus, University of California Medical School, and Professor of Medicine; Formerly Professor of Clinical Pediatrics, University of California Medical School; Formerly Visiting Pediatrician, San Francisco Children's Hospital; Formerly Member Health Advisory Board of the City and County of San Francisco; and WILLIAM E. CARTER, M.D., Director of University of California Hospital, Out-Patient Dept.; Formerly Chief of Children's Clinic, University of California Hospital; Formerly Attending Physician, Los Angeles County Hospital; Formerly Attending Physician, San Francisco Hospital, San Francisco. Published by C. V. Mosby Company. Sixth edition: 1942. Pp. 977; figures, 95.

Medical Application of the Short Wave Current. By WILLIAM BIERMAN, M.D., Attending Physical Therapist, Mt. Sinai Hospital, New York; Assistant Clinical Professor of Therapeutics, New York University of Medicine. Williams & Wilkins, Baltimore: 1942. Thoroughly revised, second edition. Pp. 344; illustrations, 87. Price, $5.00.

Handbook of Hygiene. By JOSEPH W. BIGGER, M.D., Sc.D., F.R.C.P.I., M.R.C.P. (London), D.P.H., M.R.I.A., Professor of Bacteriology and Preventive Medicine, University of Dublin, Lieutenant-Colonel, Royal Army Medical Corps. Williams & Wilkins, Baltimore: Second edition, 1942. Pp. 414; figures, 13. Price, $4.50.

Synopsis of Materia Medica, Toxicology and Pharmacology. By FORREST RAMON DAVISON, B.A., M.Sc., PH.D., M.B., Medical Department, The Upjohn Company, Kalamazoo, Mich.; Formerly Assistant Professor of Pharmacology in the School of Medicine, University of Arkansas, Little Rock: Second edition, 1942. Pp. 695; illustrations, 45 (4 color).

Textbook of Medical Treatment. Various authors. Edited by D. M. DUNLOP, B.A. (Oxon.), M.D., F.R.C.P. (Edin.), Professor of Therapeutics and Clinical Medicine, University of Edinburgh; Physician, Royal Infirmary, Edinburgh; and L. S. P. DAVIDSON, B.A. (Cambridge), M.D., F.R.C.P. (Edin.), F.R.C.P. (London), Professor of Medicine and Clinical Medicine, University of Edinburgh; Physician, Royal Infirmary, Edinburgh; Formerly Regius Professor of Medicine, University of Aberdeen; and J. W. MCNEE, D.S.O., D.Sc., M.D. (Glasgow), R.F.C.P. (London) Physician, H. M. the King in Scotland; Regius Professor of Practice of Medicine, University of Glasgow; Physician, Western Infirmary, Glasgow; Consulting Physician, Univ. College Hospital, London. Foreword by the late PROFESSOR A. J. CLARK, B.A. (Cambridge), M.D., D.P.H., F.R.C.P. (London), F.R.S.; Formerly Professor of Materia Medica, University of Edinburgh. Williams & Wilkins, Baltimore: 1942. Second edition. Pp. 1179; several illustrations. Price, $8.00.

Synopsis of Ano-rectal Diseases. By LOUIS J. HIRSCHMAN, M.D., F.A.C.S., Ex-Vice-President, A. M. A.; Ex-Chairman, Section on Gastroenterology and Proctology, A. M. A.; Ex-President, American Proctologic Society; Chairman, American Board of Proctology, Inc.; Professor of Proctology, Wayne University; Fellow (Honorary) Royal Society of Medicine; Extra-Mural Lecturer on Proctology, Post-Graduate School, University of Michigan; Proctologist, Harper, Charles Godwin Jennings, and Woman's Hospitals; Consulting Proctologist, Detroit City Receiving Evangelical Deaconess, Wayne County Hospitals, Children's Hospital of Michigan, Detroit Tuberculosis Sanitarium, Detroit. C. V. Mosby Co., St. Louis: Second edition, 1942. Pp. 315; illustrations, 182; color plates, 12.

A Textbook of Bacteriology. By THURMAN B. RICE, A.M., M.D., Professor of Bacteriology and Public Health at the Indiana University, School of Medicine. Pp. 560; illustrations, 119. W. B. Saunders Co., Philadelphia and London: Third edition, revised, 1942. Price, $5.00.

The book is practically the same as the second edition which appeared in 1938. The subject matter is treated superficially and from a practical standpoint. Recent developments in the field have not been incorporated in the book, so it would not be satisfactory as a textbook for medical students nor for practitioners who wish to bring their knowledge up to date.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.
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THE POSTERIOR PITUITARY GLAND.

THE activity and marked pharmacodynamic effects of extracts of the posterior pituitary were known long before the hormonal effects from many other glands were discovered. Yet, interestingly enough, only meager knowledge exists of the place of the posterior pituitary in physiology, while the place in physiology of many glands, the parathyroids and adrenals for example, is well established despite the fact that active extracts are of more recent origin and no more dramatic in their action. It was in 1895 that Oliver and Schafer[56] first demonstrated the vasopressor effects of pituitary gland extracts given intravenously, and in 1898 that Howell[38] showed that the effects rested in the fraction from the posterior lobe. In 1928, Kamm and his associates[41] fractionated the extract of the posterior lobe and showed a dissociation between the pressor and oxytocic actions.

Anatomic Relationships. There is some confusion in the terminology applied to the posterior pituitary gland. To clarify these points a chart demonstrating the nomenclature, as suggested by Rioch and Wislocki and taken from the paper of Heinbecker and White,[34] is given below:

MAJOR DIVISIONS AND SUBDIVISIONS OF THE MAMMALIAN HYPOPHYSIS.

ADENOHYPOPHYSIS.		
Lobus Glandularis	1. Pars distalis (anterior lobe) 2. Pars tuberalis 3. Pars intermedia	
NEUROHYPOPHYSIS.		
Lobus Nervosus (Neural lobe)	1. Infundibular process	Posterior lobe
Infundibulum (Neural stalk)	1. Infundibular stem 2. Median eminence of tuber cinereum	Neural stalk together with sheath of lobus glandularis, designated as hypophyseal stalk

Histologically, the structures of the neurohypophysis consist of a group of cells, the pituicytes, which are closely related to neuroglia, and large masses of unmyelinated nerve fibers. A close relationship between the hypothalamus and the neurohypophysis seems evident.[2] Fibers originating in the supraoptic nucleus pass to the neurohypoph-

ysis, and Heinbecker and White,[34] in a careful study in dogs, concluded that the only nuclei unquestionably contributing fibers were the supraoptic and paraventricular. These relationships are most important in the consideration of diabetes insipidus to follow below, and further discussion concerning them will be found there.

Hormones. There has been much dispute concerning the origin of the hormones. For a long time reluctance to accept the neural elements as a source of glandular secretion upheld the intermediate lobe as the source. However, much evidence has accumulated to indicate that the neural elements, the pituicytes, are the source of the vasopressor, oxytocic and antidiuretic activities,[7,25] whereas intermedin, the melanophore-dispersing hormone, comes from the intermediate or anterior lobe.

The chemical nature and actual number of the hormones are as obscure as their origin. The pressor, antidiuretic, oxytocic, and melanophore-dispersing principles are generally conceded to be separate entities. As just stated, the last named is thought to be from the median, or anterior, lobe, while the others are clearly posterior in origin. Likewise, from what has been said, it is clear that extracts have not been purified chemically. Best known of the highly purified fractions are the vasopressor and oxytocic principles separated by Kamm and his associates[41] and by Stehle.[65] Electrophoretic studies[14,39] indicate different rates of migration of pressor and oxytocic principles obtained from chemically untreated, mechanically expressed juice of fresh glands, and lend evidence to the idea that they are, in their natural state, separate chemical entities. Sedimentation by the ultracentrifuge[61] indicates the large molecular size of these fractions, which exist either as a single large molecule or two separate large molecules, and also indicates a change in these structures by the technique of extraction, with the development of physiologically active split products.

The dramatic pharmacodynamic effects of the hormones of the posterior pituitary have led to widespread use of the extracts of the gland. In the United States Pharmacopœia XI, the preparation listed is Solution of Posterior Pituitary, or Posterior Pituitary Extract (PPE). The action of this preparation is striking, especially on the renal, cardiovascular, and gastro-intestinal apparatus, as well as on metabolism, the lungs, the uterus, and on carbohydrate metabolism. It acts directly upon smooth muscle. Each one of these actions will be discussed below; and diabetes insipidus, because of its importance, will be considered as an entity following these discussions. The important clinical relationships are considered under each heading.

Renal Action. It has been suggested that the antidiuretic effects of PPE are generally associated with the pressor principle, and indeed the effect is shown clearly by pitressin. Some evidence points to the possibility that a separate principle, or at least one which may be dissociated from the pressor effect, may be responsible. Heller,[35a] by use of thermal inactivation at various pH values, showed that vasopressor effects are lost at a more rapid rate than the antidiuretic effects. By making use of the difference in stability of the antidiuretic and vasopressor principles, he obtained preparations which contained only about 8 parts of pressor activity to 100 parts antidiuretic activity. These had the typical action of PPE on water diuresis and on the urinary chlorides of normal human subjects.

The renal effects of PPE are clear-cut. Ten units, 1 cc. of the so-called obstetrical preparation (1 unit equals the activity of 0.5 mg. of the standard powder), produces a marked reduction in urinary volume in normal individuals in the face of a high water intake.[58,64] Similar effects occur in renal disease and diabetes insipidus, and the same inhibitory action is elicited in animals.[52,63b] Present evidence points strongly to a primarily renal mechanism—increased reabsorption of water by the tubular mucosa, especially the proximal convoluted tubules and the thin portion of Henle's loop.[10,26,63a] The other proposed theory is that of an extrarenal action on water exchange between blood and tissues. In some vertebrates, the bird for example, the quantity of glomerular filtrate is affected.

Increased reabsorption by the tubules has been related to the structure of the nephron in various vertebrates,[10] and has been correlated with the development of the thin segment of the loop of Henle. Interesting in this light is the work of Heller.[35c] He made a quantitative estimation of the antidiuretic activity of pituitary in a number of classes of vertebrates, mammals, birds, amphibians, teleost and elasmobranch fishes. Antidiuretic activity was present in the pituitary glands of all these groups, and in different species of the same class of vertebrates the glands were found to contain roughly the same amount of antidiuretic activity per 100 gm. of body weight. There was, however, a pronounced difference in the content in mammals and all other classes. Mammalian pituitary bodies contained at least 8 times as much antidiuretic principle per 100 gm. of body weight as the glands of non-mammalian species. A relationship was suggested between the phylogenetic development of Henle's loop and the amounts of antidiuretic hormone produced by the posterior pituitary, and a correlation of the development of an anatomic structure with that of a hormonal mechanism. Accompanying the reabsorption of water there is an increase in chloride output[57] attributed to a decreased tubular reabsorption of that ion.[63a]

Certain conditions are known to influence the antidiuretic action. Boyd and Garand[9] found that extremes of environmental temperature depress the water-retaining effects of PPE in rats. Water retention was more effective after prolonged dehydration and thirst. Administration of salt decreased, and even reversed, the water-retaining effect. Hickey, Hare and Hare[36] have shown that the state of body hydration influences the antidiuretic potency of the posterior lobe in rats. Dehydration diminishes the potency. They reviewed the literature on this subject.

The renal action of PPE is often described as the diuretic-antidiuretic action. There is much controversy concerning the diuretic action, and evidence points strongly to its being a secondary effect from pressor activity.[35b] A diuretic hormone from the anterior lobe has been postulated, but Barnes, Regan and Bueno[3] believe this effect results through thyroid stimulation, for it is inhibited by thyroidectomy in dogs.

Clinical uses of posterior pituitary extracts based on the antidiuretic effect have found an important place in the treatment of diabetes insipidus, and will be discussed under that subject. Recently attempts have been made[57,58,64] to utilize the antidiuretic effect in concentrating the urine for a test of renal function. Results appear promising. Ten

units of PPE are given to an unprepared patient and 3 hourly collections of urine made. Normally, the specific gravity of one specimen reaches, or exceeds, 1.022. Pregnancy, marked oliguria, and hypersensitivity to PPE are contraindications. The test should be used with caution in patients with angina pectoris. (See Cardiovascular Effects.)

Cardiovascular Effects. These effects need little discussion from the clinical standpoint. Inspection of the patient following the injection of 10 units of PPE shows a distinct pallor, which can be interpreted only as the result of constriction of small vessels contributing to skin color. One would expect definite changes in the blood pressure, but such doses in man produce very little change.[51,64] In animals, the effects on blood pressure vary with many factors. In dogs, for example, marked rises occur, but the effects of coronary constriction may produce a decided drop. The studies of Grollman and Geiling[32] indicate for a brief period a fall in pulse rate, O_2 consumption, and cardiac output, followed by a rise. These primary effects are interpreted as resulting from coronary artery constriction; the secondary effects from the accumulation of catabolites,[48] which brings about a condition of oxygen debt.

The importance of considering the results of coronary constriction must be kept in mind when PPE, or pitressin, is given to patients with arteriosclerotic heart disease. Where angina pectoris is the clinical manifestation of coronary arteriosclerosis, one would have the best clinical test of the importance of this effect and, indeed, if the drug is given to such patients, it should be administered with caution and with the antidote, epinephrine or ephedrine[48,49] at hand. PPE has been known to produce attacks of angina in patients with coronary arteriosclerosis. The Reviewer has administered 10 unit doses of PPE many times, without any harmful effects, to patients with coronary arteriosclerosis. Graybiel and Glendy[29] have found no significant cardiovascular symptoms in patients with arteriosclerotic heart disease with angina after slow intravenous infusion of a dilute solution of pitressin in doses adequate to produce pallor and uncomfortable abdominal cramps.

Electrocardiographic changes resulting from administration of PPE have been described[32,48] and are thought to arise through stimulation of the cardio-inhibitory center, through vasoconstriction and inhibition of oxidative processes.

In spinal anesthesia[13] posterior pituitary has been used with ephedrine to prevent a drop in blood pressure.

Attempts to relate posterior pituitary activity to hypertensive states, including toxemias of pregnancy, are considered under Hyperfunction, below.

Effects on the Gastro-intestinal Tract. These effects depend largely upon the action on smooth muscle. In man there is an inhibition of gastric motility and a depression of gastric secretion following the administration of PPE. In diabetes insipidus,[6] gastric symptoms are frequent. Changes in the gastric juice have been noted, including a higher degree of acidity, and a greater volume. Administration of PPE decreased these findings. In animals, gastric erosions and ulcers have been produced by the administration of pitressin, or PPE.[5,21] Local ischemia is the usual explanation.

Other evidence of a relationship between the posterior pituitary and gastric ulcer has been the finding of ulcer in association with pituitary

disease. The fact that PPE inhibits gastric secretion has led to its use in the treatment of peptic ulcer, while the association of gastric erosions with injections of extracts in animals has led, as stated above, to the idea of an etiologic factor for peptic ulcer in vasospasm, if not in the posterior pituitary. Interestingly enough, both of these concepts were discussed in succeeding issues of a recent journal.[5,50]

Reports in the literature do not agree upon the effects of PPE on the intestine. Some of these differences are accounted for by variations in species, in technique, and in the part of the gastro-intestinal tract studied. In unanesthetized dogs, Larson[45] found that PPE, or pitocin, in intravenous doses of 10 milliunits per kilogram usually produced a decrease in tone and motility of the upper and lower portions of the large intestine; larger doses produced similar but more marked changes. Pitressin usually had no effect. Subcutaneously PPE and pitressin in larger doses usually caused an increase in movements in the upper portion of the large intestine with no significant effect on tone. In half the cases the lower portion was not affected. Pitocin subcutaneously in like dosage usually had either no effect or decreased the tone and motility of the large intestine.

In man, during operations on the abdomen,[11] marked spasm of the intestines with a concomitant peritoneal relaxation has been noted within 5 to 10 minutes after the intramuscular injection of pitressin. This effect is manifested in the usual patient by the act of defecation.

A number of uses have been found for PPE in the gastro-intestinal tract. These include the reduction of intestinal flatus in gall bladder visualization by Roentgen ray[43] and the control of postoperative distention.[11,59]

Effects on Carbohydrate Metabolism. Hyperglycemic effects have been attributed to the oxytocic fraction,[22,37] and it has long been known that PPE inhibits the hypoglycemia of insulin injections.[22,31] Griffiths has studied this problem but finds no satisfactory answer. A direct relationship or antagonism is possible, or circulatory changes in the skin could decrease the absorption of insulin. Griffiths[31] found that PPE inhibits hypoglycemia from subcutaneous insulin in rabbits, but in many animals the intravenous administration of insulin gave inconstant results. This suggests definitely the theory of decreased rate of absorption brought about by the vasoconstrictor effect of PPE.

Neufeld and Collip[54a,b] brought forward evidence in rabbits and other animals to show the existence of a substance from the posterior lobe, not the pressor or oxytocic principle, which is antagonistic to the hyperglycemia caused by epinephrine.

Effects on Respiration. Laryngospasm, bronchoconstriction, and increased mucous secretion have occurred, especially in asthmatic individuals during anesthesia following pitressin.[11] Respiratory effects are described[25] as secondary to circulatory effects.

Effects on Blood. The pressor hormone causes hydremia or dilution of the blood,[59] with a fall in hematocrit, a decrease in specific gravity, and in total serum proteins.

Corey and Britton[15b] have shown an antagonistic action of desoxycorticosterone and PPE on chloride and water balance. This report elaborates on former communications on the same problem from the same laboratory. In animals desoxycorticosterone was found to reduce

severely the output of urinary sodium, while PPE greatly increased its excretion. The authors feel that removal or deficiency of either corticoadrenal or posterior pituitary tissues may produce disturbances in fluid and salt balance explicable on the basis of the remaining glands being unleashed or hyperactive. Both glands elaborate principles which specifically counteract or antagonize each other in their effects on fluid and electrolyte balance. For normal salt and water regulation in the body, a balanced relationship between the adrenal and pituitary mechanism seems essential.

Anemia is produced experimentally[19,28] and is discussed further under Hyperfunction.

Effects on the Uterus. Geiling and Oldham,[25] in reviewing the evidence in the literature on the *in vitro* and *in vivo* experiments on the uterus, outline as follows the factors upon which the nature and degree of the reactions depend: (*a*) The species of animal; (*b*) the phase of the menstrual or estrous cycle; (*c*) whether the uterus is gravid or not gravid; and (*d*) the stage of pregnancy, whether early, late, in parturition, or in the puerperium. They point out that the reaction of the uterine muscle to pituitary preparations is markedly affected by the nature of the ovarian, placental, or anterior pituitary hormone whose influence is preponderant at the time of injection.

In human beings early in pregnancy, there is no reaction to pitocin, probably because of inhibition by the luteal secretion; there is a response to pitressin. Later in pregnancy, the reaction to pitocin returns. In parturition, the uterus is very reactive to pitocin and to PPE, a time when their use by obstetricians is widespread. In the puerperium again, there is little or no response to pitocin. This summary is taken from Geiling and Oldham.[25]

Murphy, using the Lóránd tocograph, has studied variations in uterine response to PPE in certain stages of pregnancy. In one study[52a] on 26 primagravidas, approximately 19 days before the onset of labor, PPE was given intramuscularly in small doses. Murphy correlated the responses with the duration of labor and found significantly shorter labors in those with a response. Under the conditions of his study he concluded that there existed a significant relationship between the character of the uterine contractile response to PPE, administered during late pregnancy, and the character of labor, as indicated by its length. In another report, the same author[52b] studied 32 women with the same technique at regular intervals during pregnancy. In 2, a uterine response failed to develop at any time; in 29, a characteristic reaction occurred; and in 1, an unusual response was recorded. Typical responses included: 1, A series of clonic contractions at a rate of 20 per hour; 2, onset of contractions after the 25th week of gestation; 3, a wide variation in the time in pregnancy when contractions were first observed; 4, inconsistency with respect to appearance of contractions after they were first noted; 5, a shortening of the interval between treatment and onset of uterine response as pregnancy advanced; 6, a slowing of the contraction rate as pregnancy advanced; and 7, absence of unusual tension of the uterine wall before treatment. He concluded that patients vary widely in their response (uterine) to pituitrin during pregnancy; contraction patterns depend largely on the tension of the uterine wall.

The human non-pregnant uterus shows, surprisingly enough, a greater response to pitressin than to pitocin. Variations also occur in the different phases of the menstrual cycle. Interesting studies on the rabbit uterus[8] show striking differences in sensitivity of different parts of the uterus to epinephrine and PPE. There is a relative insensitivity of the cervical end to PPE and sensitivity to epinephrine. The tissues in these studies were taken from uteri shortly before and shortly after parturition.

A preparation with such marked pharmacodynamic effects as PPE cannot escape widespread use. It has been used in all phases of pregnancy for over 30 years and hazardous results have been reported from the beginning.[53] In the first and second stages of labor, great danger to mother and child may develop with its use. Complications such as ruptured uterus, lacerated cervix, fetal death, and others have curbed its use in the induction of labor. After the second stage, it is widely used to shorten the placental stage and decrease bleeding, to hasten, if possible, involution and prevent infection, a point not entirely agreed upon,[25] and to prevent or control hemorrhage in therapeutic abortion. Conservatism requires that its use then be confined to hospital practice.

Hypersensitivity to PPE. Hypersensitivity to PPE has been reported on several occasions.[47] Symptoms include pallor, a drop in blood pressure, gasping respiration, urticaria and edema. The dramatic picture is relieved by epinephrine. So-called "pituitrin shock" is also infrequent, but not rare.[1] Adelman and Lennon noted 7 cases in 1 year. They frequently found pruritus, urticaria, and angioneurotic edema accompanying the shock.

Theories of the cause of pituitrin shock include histamine reactions, anaphylaxis, and cardiac effects. The preparations used by Adelman and Lennon are reported as histamine-free. A cardiovascular etiology is conceivable, for the effects of PPE on the coronary arteries could result in coronary constriction, myocardial anoxia, cardiac dilatation, and the picture of shock. However, the occurrence of urticaria and of positive skin tests for sensitivity to the preparation favors an allergic explanation. Skin reactions are apparently the result of some fraction other than the pressor or oxytocic principle.

Treatment of pituitrin shock includes intravenous fluids, oxygen, and epinephrine or ephedrine. The latter two drugs are effective in allergic states and, as stated before, in coronary constriction. They are contraindicated, however, in certain types of anesthesia, notably ether and cyclopropane,[1] when they should be omitted in treatment. Pituitrin shock has developed in patients under anesthesia, especially in the obstetrical use of PPE, as well as in its use in gynecologic surgery.

The physician administering PPE should be cognizant of these dangers and should be prepared for their treatment.

The Melanophore-dispersing Hormone. The dermal melanophore-dispersing hormone, so-called intermedin, is a product of the intermediate lobe. It causes pigment migration when injected into cold-blooded vertebrates. In mammals, which have no chromatophores, its importance is not established, but a metabolic rôle has been suggested. The origin and functions of this hormone are discussed by Kleinholz and Rahn.[44]

Clinical Syndromes Related to Posterior Pituitary Dysfunction. Studies of the pharmacodynamic effects of PPE have not been accompanied by a clarification of the syndromes thought to be associated with posterior pituitary dysfunction. In most glands of internal secretion where functions have been ascertained, syndromes associated with hyper- and hypofunction are well known. This is not true with the posterior pituitary gland.

The Question of Hyperfunction. A large literature exists[46] on the possible relationship of pressor substances, particularly that concerned with the posterior pituitary, to eclampsia and other hypertensive states. No consistent findings have been reported. In the presence of eclampsia, or preëclampsia, doses of PPE already mentioned as not appreciably affecting the blood pressure produce sharp elevations in blood pressure,[17,18] and diminish the urinary volume. The observation that preëclamptic women show such sensitivity while normal pregnant women do not has been the basis for a test to differentiate preëclamptic states. A positive test in the last trimester would lead to the assumption of the presence of preëclampsia. In 113 women, de Valera and Kellar[17] did not think the results sufficiently consistent to justify the use of the reaction as a diagnostic test for preëclamptic toxemia. Although such reactions suggest the possibility[18] that the posterior pituitary gland may, in some way, be associated with the disease, inconsistency in the reactions speaks against an important relationship. In other hypertensive states, similar associations have been postulated. Differentiation between pale and red hypertension on the basis of these reactions has been suggested, but this view does not represent the consensus.

Friedman and Prinzmetal,[23] using the denervated rabbit's ear sensitive to epinephrine in 1 to 100,000,000 dilutions and to pitressin in 1 to 150,000, found only 2 of 18 hypertensive patients with evidence of pressor activity in the blood exceeding that of those with normal blood pressure. Again results are conflicting and inconclusive. Certainly, posterior pituitary secretion may be important in such conditions when it reaches hyperactive structures, where deactivation does not occur, or where excessive amounts are put out, but proof for this point is not yet established.

Liu[46] points out that experimental hyperfunction produced by injection of hormones has been successful in a number of glands, such as the parathyroid and the islands of Langerhans. To be sure, this method has been used with the posterior pituitary. Injections in animals have produced the changes already mentioned (*v. supra*). To repeat, hypertensive pictures and gastro-intestinal changes develop. The latter findings include engorgement of the stomach with development of erosions. Some animals develop punched-out ulcers, at times even with perforation. Erosions of the stomach occur in many animals, and neutralization of the gastric acidity prior to the injection of the pituitary extract prevents the development of the lesions.[19] It is the pressor principle that is gastrotoxic and the gastric effects apparently result from intense vasospasm with inhibition of blood flow.

Further remarks on gastric effects will be found under Diabetes Insipidus and under Effects on the Gastro-intestinal Tract.

Anemia of the macrocytic variety has been produced in rabbits by

large subcutaneous doses of PPE.[19,28] It has been ascribed to increased blood destruction because of the accompanying reticulocytosis and increased bile elimination. Water retention has also been given as a cause,[28] but the problem is not settled.[20]

PPE in large doses affects the kidneys, apparently through angiospasm of the renal arteries and arterioles.[46] Byrom[12] believes the changes in rats resemble those of eclamptic toxemia, with hypertension, delayed excretion of water, albuminuria, coma, catarrh and degeneration of the renal convoluted tubules. The parallel is interpreted as supporting the view that the lesions of eclampsia and preëclampsia are expressions of vascular spasm, but the hypothesis is rejected that such spasm is caused by simple oversecretion of vasopressin. Liu[46] points out the doubtful clinical significance of data such as the animal experimentation cited above. One would be on uncertain grounds in postulating that certain cases of peptic ulcer, macrocytic anemia, or renal disease result from hyperfunction of the posterior lobe. Dosage in the experimental animals has been tremendous. It is possible, as has often been stated, that the body may become more sensitive to posterior pituitary hormones and, in eclampsia for example, may react markedly to small amounts.

Jones[40] has described a syndrome which he considered was due to overactivity of the posterior pituitary. The patient showed hypertension, hyperchromic anemia, achlorhydria, and abnormal carbohydrate tolerance. An extract of the patient's urine disclosed a pressor principle,[55] an antidiuretic action on the rat, and presence of the melanophore-dispersing hormone. The effects of the extract were similar to those produced by the pressor principle of pituitary preparations. The pressor and antidiuretic substances in the urine very noticeably decreased with improvement of the patient.

The Question of Hypofunction—Diabetes Insipidus. Diabetes insipidus is generally considered as the outstanding expression of posterior lobe hypofunction. This condition is characterized by polyuria with a urine of low specific gravity and an increased thirst. A possible rôle of the anterior lobe in diabetes insipidus has been put forward, but all evidence points directly to the neurohypophysis.[2,15a,25]

Dandy[16] states that diabetes insipidus in man is caused by lesions in the environs of the hypothalamus and is pathognomonic of a lesion of some type in this general area, but that the present limits of the center are not established. Clinically, difficulties in establishing these limits lie in lack of localization of disease to areas sufficiently small; and, experimentally, difficulties also lie in localized damage, for surrounding structures may be injured. Dandy states as clinical facts that hypophyseal tumors confined to the sella turcica and not affecting the stalk or hypothalamus never induce diabetes insipidus, regardless of hypophyseal destruction, and operations on the human hypophysis for tumors are never followed by diabetes insipidus unless the stalk or base of the brain is traumatized. Still PPE usually controls the symptoms. Dandy quotes a case of Futcher's[24] in which a small tumor at the base of the brain did not involve the hypophysis, and a case of his own in which section of the hypophyseal stalk without trauma to the base of the brain or hypophysis produced permanent polyuria and polydipsia.

In the rat[27] experimental diabetes insipidus results when fibers which innervate the parenchymatous cells of the neurohypophysis are destroyed, releasing the cells from nervous control. The cells atrophy, and when the number of inactive cells is large, compensatory hypertrophy appears. If enough secretion is produced, diabetes insipidus is only temporary. If not, persistent mild diabetes insipidus ensues. If the hypertrophied cells secrete to exhaustion, permanent diabetes insipidus appears.[27] In dogs,[34] diabetes insipidus results from complete interruption of the fibers to the neurohypophysis or from complete destruction of the neurohypophysis with only 3% to 10% of the pars distalis remaining. Maximum permanent diabetes insipidus may not result with failure to interrupt all fibers to the neurohypophysis or failure to remove it completely. These authors feel that confusion on this point results from failure to recognize that complete removal or denervation of the median eminence is a necessary condition for maximum permanent polyuria. They also present evidence that the cells of the supraoptic and paraventricular nuclei do not secrete pitressin, and that infection in the region of the hypothalamus can prevent the manifestations of diabetes insipidus, even in the absence of the entire neurohypophysis.

Others[2] indicate that injury to the supraoptico-hypophyseal tract leads to atrophy of the neurohypophysis and that interruption of these nerve tracts produces degenerative changes in the pituicytes with the occurrence of symptoms of diabetes insipidus. Diabetes insipidus has been produced in many animals by interruption of the hypothalamico-hypophyseal tract in the posterior lobe, in the stalk, or at the supraoptic nucleus. Maximum and permanent diabetes insipidus follows removal or complete denervation of the entire neurohypophysis resulting in retrograde degeneration of the entire supraoptic nuclei and the rostral ventral portions of the paraventricular nuclei. Failure to interrupt fibers of even 15% of the cells innervating the neurohypophysis will prevent the development of permanent diabetes insipidus.

The necessity for participation of the anterior lobe in the development of diabetes insipidus is debated. In 9 dogs, Heinbecker and White[34] showed, by microscopically confirmed serial sections, that permanent diabetes insipidus followed complete destruction of the neurohypophysis with complete absence of the pars distalis. They feel that the view, based on clinical reports, that some tissue of the pars distalis is necessary for diabetes insipidus, is due to the fact that the median eminence probably remained. A phase, called normal interphase, exists in some experimental animals when fluid exchange approaches normal between the transient and permanent phases of polyuria. This was eliminated in animals when all pitressin-secreting tissue was removed. Heinbecker and White suggest that normal interphase results in injury to pitressin-forming tissue sufficient to prevent hormone secretion, leading to the development of transient polyuria. After the effects of trauma subside, secretion is resumed, to disappear again when degeneration of the pituicytes occurs. This sequence of events would divorce any explanation for normal interphase from the pars distalis.

Information such as the above indicates that, in the dog, the adenohypophysis is not necessary for the development and maintenance of a permanent diabetes insipidus. Keller[42] also demonstrated in dogs that

a moderate diabetes insipidus can exist in the absence of the anterior lobe and indicated that the absence of diabetes insipidus following any hypophysectomy is evidence that functional antidiuretic secretory tissue remains intact. He suggests that the presence of a functioning anterior lobe may intensify the severity of the diabetes insipidus. Some of Heinbecker and White's data do not support this view. Baker and Craft[2] report a case with only about one-sixth of the anterior lobe remaining in the presence of severe and permanent diabetes insipidus. The anterior lobe deficiency was sufficient to give dwarfism.

In diabetes insipidus, polyuria and polydipsia are the characteristic symptoms. The question of which is primary, of whether increased urinary output follows thirst, or thirst water-loss through the kidneys, is important in understanding the mechanism of the disease. Richter[60] obtained evidence in rats to show that polyuria preceded the polydipsia and is the primary factor. The renal nerves play no part in the production of water diuresis in hypophysectomized dog.[4]

In transient diabetes insipidus, a substance has been found in patient's serum which inhibits the antidiuretic activity of PPE.[62] This was not found in 2 patients with chronic diabetes insipidus. The urine of dehydrated normal dogs contains an antidiuretic substance; that of dehydrated dogs with diabetes insipidus, none.[33]

From an investigation in patients with diabetes insipidus of the chloride and water intake and output with and without pitressin, White and Findley[68] concluded that there is no justification for division of cases into hyperchloremic-hypochloruric and hypochloremic-hyperchloruric types, or for the view that the condition is primarily a disturbance of the processes of exchange of water and salt between tissues and blood.

Nothing will be said here concerning standard forms of treatment with parenteral pitressin or PPE or the insufflation of powders into the nose. These forms of treatment are not always satisfactory because of side reactions, local irritation, gastric distress, and other symptoms. Therapy aiming at delayed absorption has been tried, as in the case of protamine insulin in diabetes mellitus or pellet therapy in Addison's disease. The object is delayed absorption with constant quantities which meets physiologic requirements.[67] Although inunctions have been tried, success has been outstanding with pitressin in oil subcutaneously.

Greene and January[30a,b] implanted pellets of dried PPE in animals and patients. Inflammatory reactions limited their use. Pitressin tannate in peanut oil was then tried and was successful both in animals and patients. With 5 pressor units to the cubic centimeter, 1 cc. doses ameliorated symptoms for 30 to 82 hours. There were no unpleasant or deleterious general or local reactions. The effect on the manifestations of the disease was equal to that of other preparations of PPE and without disagreeable side effects. Stephens[66] found that 0.1 % zinc acetate prolonged and intensified the effect of aqueous solutions of pitressin, but that pitressin in oil gave a more marked prolongation and intensification of the effect.

Thorn and Stein[67] also tried pitressin tannate in oil. They found in 3 patients that a dose of more than 0.25 to 0.30 cc. daily should not be continued unless the clinical condition of the patient is being followed

closely. Larger doses may be given safely when treatment is administered only once in 48 hours. Control of polydipsia and polyuria was most satisfactory with treatment once daily. Pitressin tannate settles out of oily solution so that the preparation must be shaken vigorously when used. Failures in treatment have occurred without this precaution. Complications in Thorn and Stein's hands were water intoxication with excessive dosage and increase in the amount and duration of the menses in 2 patients.

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NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF
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REVIEW OF SHOCK THERAPIES FOR THE MENTALLY ILL.

SINCE the introduction of insulin, metrazol, and electric shock in the treatment of the mentally ill, a tremendous amount of work has been done with these procedures. This work has not been confined merely to the treatment and results of the methods from a psychiatric viewpoint, but has produced far-reaching investigations by workers in allied fields of medicine. For instance, the physiologist has become interested in the mechanism which produces the coma; the biochemist is interested in studying the various chemical changes which take place during therapy; the neuropathologist is concerned with the pathologic changes that occur during and after the therapy; the internist is concerned with the problem of "punishment" that the body is forced to absorb during the actual treatment; the psychologist is absorbed in following the psychologic changes which take place under the influence of the treatment; the orthopedist desires to know the type of fractures occurring during insulin, electrical and metrazol therapy; the neurologist studies the influence of these therapies upon the organic nervous system; and the psychiatrist attempts to explain the manner in which the psychosis is altered.

The interest in this subject is testified to by the large bibliography which has been developed within the past 6 years. Jessner and Ryan[30a] report 353 individual articles in their recent book, *Shock Treatment in Psychiatry*. The yearbook *Neurology, Psychiatry, and Endocrinology* has abstracted 68 articles since the treatment began in 1936.

Even though the original enthusiasm associated with the use of shock therapies has not been sustained, there is ample evidence that these treatments will continue to exert a certain amount of influence upon therapeutic procedures in the psychotic groups until newer methods of greater efficacy are introduced. One cannot say that the therapy offered the schizophrenic prior to the use of shock therapy was impotent; however, whatever therapy was used it was certainly less dramatic

in its immediate results. Psychotherapy, at best, is a slow and tedious procedure, and in some institutions utterly lacking. The introduction of a tangible, easily administered therapy was grasped by many. Such procedures have been adopted in private clinics, psychopathic and state hospitals. Not all the work by these various groups has been reported, but a considerable amount of this work has been published.

We[55] have recently analyzed 239 articles published in 39 English language medical journals during the past 6 years. We found that shock therapy may be roughly classified as follows (figures in parenthesis indicate the number of publications dealing with the topic listed):

1. General discussions on the use and results of insulin, metrazol, and electric shock (92).
2. Technique of administration and general management (22).
3. Complications (24).
4. Electrocardiographic and electroencephalographic findings (7).
5. The *modus operandi* (13).
6. Psychologic factors (12).
7. Follow-up studies and prognostic factors (6).
8. Physiologic, pharmacologic, pathologic, or biochemical aspects (34).
9. Neurologic effects (7).
10. Miscellaneous factors (20).

For our present discussion we have attempted to review the literature available to us on all these topics except items 8, 9 and 10.

General Discussion on the Use and Results of Insulin, Metrazol and Electric Shock. We[55] found that about one-fifth of the papers[52] are concerned with the results of therapy, and of this number about 30 express a favorable opinion regarding the efficacy of the treatment. The others end on a vague note of optimism and suggest continued experimentation in this field. In only 1 paper[37] did the author feel that insulin treatment had not been proven. On the contrary, he raised considerable doubt as to its value.

Reports upon the results of therapy vary widely. In the first place the number of cases reported varies from 1 to 1039 per paper. Of the 50 papers, 33 report results on less than 100 cases, and are markedly optimistic on the basis of a small series. Recovery rates are reported from 92.3% to 7%, with an average of 52%. It is probably unsound to compare too closely the recovery rates on any two sets of studies from different hospitals since the criteria and definitions of "recovery" are individual with each hospital. In this connection we agree with Low[38] who states that recovery rates are reliable only when studied in relation to the adjustment of the patient after discharge.

In general most workers reporting seem to agree that the following factors are necessary for the most satisfactory results from shock therapy: 1, An illness of acute onset and short duration, preferably under 6 months, not longer than 1 year. 2, The presence of affective factors in the psychosis. 3, An adequate prepsychotic personality. 4, The presence of exogenous, as opposed to endogenous, precipitating factors. 5, An attempted heterosexual adjustment. 6, The absence of hallucinations and dereistic thinking.

The literature dealing with the general discussion of these therapies is interesting in that the authors attempt to confirm or disprove the

efficacy of these therapies. On the whole there is a fairly optimistic tone sounded in favor of these treatments. As Nation[43] reports, ". . . . in this modern day every patient is expected to receive some form of therapy where possible, rather than depend on spontaneous remission." Sakel unwittingly spanned a gulf which some have felt existed between psychiatry and the rest of medicine by the introduction of insulin therapy. In this connection Sakel[56] states, ". . . . it has become apparent that in the solution of these problems (of insulin therapy) psychiatry will be brought to medicine and medicine will come to psychiatry."

The belief that insulin is of benefit in the treatment of the schizophrenic is expressed by Easton[13] who states, "It appears to me that in insulin we have a drug by means of which we can alter the clinical picture in schizophrenia. Whether the treatment ever becomes established time alone will tell. I do not believe the drug is specific in its action, but it seems to affect the patient in such a way as to make him more accessible and hence responsive to other recognized forms of treatment, such as occupational and psychotherapy. The latter are very necessary adjuncts to the treatment. The personality of the physician and nurse will both be reflected in the results obtained. I am firmly convinced that one can do more for schizophrenics with insulin than is possible without it."

Young[66] expresses his opinion after using insulin and metrazol for 3 years by saying, "It must be said that this brief and superficial accounting of experiences with the newer pharmacologic methods of treatment in the schizophrenic and depressive psychoses shows them to be a valuable adjunct and an advance in therapy. . . . . In the schizophrenic groups insulin or metrazol, or a combination of the two, are effective therapeutic agents, but it should be emphasized that the patient must be treated early. . . . . Metrazol has been particularly effective in the treatment of the depressive reactions. . . . . Finally, no matter how striking the results of any special method, treatment must continue along broad lines which focus the interest of the physician upon the patient and his adjustment to life situations, past, present, and future."

Early in 1936, Wortis reported upon the use of insulin therapy, and concluded with the remark, "The insulin treatment of schizophrenia promises to be either an unusual medical fiasco or a most remarkable discovery." Some 15 months following this statement Wortis[65a] felt the latter prediction was more likely to be true.

The general "feeling" that insulin is of value has been expressed by Strecker[61] in his statement, "While keeping in mind that after a certain duration of illness good results are obtained in a minority of cases, the results obtained in the first year of illness, at any rate, and probably also in the second, indicate that there is some real value in insulin treatment. It is only natural that those who have seen many new treatments come and go should wish to reserve their judgment, but I believe that most of those who have used or witnessed this therapy themselves cannot help feeling that it does constitute a decided advance in the treatment of schizophrenia."

Ross[52] summarizes the results of both insulin and metrazol therapy as follows: "Beneficial results from treatment of all cases of dementia præcox of no matter what duration with insulin are much greater than

the results of the untreated group. The results of treatment with insulin are much better than the results obtained from cardiazol alone. Combination of cardiazol with insulin apparently assists the action of the insulin in selected cases. Treatment with camphor is not recommended by those who have used it in New York State Hospitals. The results obtained in cases where the duration is over 2 years not only justified the expense and time, but show it would be an error to neglect such cases. The recovery and improvement rates are progressively less according to the duration of the illness. The dangers of insulin therapy in the hands of experienced and trained physicians are almost negligible. An active educational campaign should be carried on, so that an early diagnosis of dementia præcox can be made and treatment instituted at the earliest possible date."

Bond, Hughes and Flaherty[9] concur in these favorable impressions, but they sense the necessity of follow-up, and something of the difference of opinion that arises in establishing the diagnosis of schizophrenia. They report, "In every hospital using insulin-shock, the patients treated should be followed for 5 years. Another group of patients, or other groups, as near alike as possible should be followed for the same time as controls. It seems certain that relapses after favorable responses will follow in all groups. In the valuable paper just published by Malamud and Render it is stated that a study of the course and prognosis in schizophrenia should include the criteria used by the author in diagnosis. We take a little exception to this statement because it might give encouragement to more varying personal standards for schizophrenia. After all, it is safer for the psychiatrist to use the criteria put down in the official *Statistical Manual*, and to work toward a definition which all can use. Insulin-shock therapy is not a complete answer. But the transformation of the patient's condition is so immediate and favorable in a majority of cases that it will have place in, or provide suggestions for, a further therapy, and this without regard to whether good results last for an afternoon or indefinitely. It is only fair to remember that Sakel spoke of insulin-shock as the artillery in a general combined attack on the disease process. Insulin in convulsive doses alters the metabolic processes of nerve."

The reports thus far cited have dealt with the physicians' ideas about the therapy. It is interesting to learn what the patient has to say about the treatment. Starks[60] has reported that patients ". . . . receiving insulin have little if any objection to the treatment and have no memory of a fear reaction. All but a small percentage of patients receiving metrazol find the treatments unpleasant and object to them in varying degrees. Of the metrazol-treated patients, one-fourth admitted fear of death in connection with the injections. All but 6 of the 47 patients receiving metrazol recognized that they were being treated for their sickness. These 6 interpreted the treatment as punishments. In many of those experiencing a fear of death and in all who regarded the treatments as punishments, it was possible to correlate these reactions with previously existing morbid trends. Both drugs, whether used solely or successively, give rise to a feeling of increased physical vitality, reduce emotional tensions, promote lucidity and a realistic outlook on life, and assist in reintegrating intrapsychic and

ERRATA

Page 141—Heading *should read:*

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Page 142, 37th line—*reads:*
from 92.3% to 7% with an average of 52%.
Should read:
from 7% to 92.3%, etc.

Page 147, 38th line—*reads:*
extensive treatment with thiamin bichloride, etc.
Should read:
extensive treatment with thiamin chloride, etc.

Page 147, 42nd line—*reads:*
administration of protamine, etc.
Should read:
administration of potassium, etc.

Page 148, 17th line—*reads:*
collapse, and changes in the control nervous system, etc.
Should read:
collapse and changes in the central nervous system, etc.

Page 148, 21st line—*reads:*
The death rate from shock therapies shows a low incidence of 23 per 10,000 patients, etc.
Should read:
The death rate from shock therapies shows a low incidence of 73 per 10,000 patients, etc.

Page 148, 11th line from bottom:
Reference No. 42 should be No. 44.

Page 149, 30th line—*reads:*
tion, auricular extrasystoles, shifting forewaters, etc.
Should read:
tion, auricular extrasystoles, shifting pacemaker, etc.

Page 152—References:
Reference 11 *reads:* Cleckley, Bowles and Metter; *should read:* Cleckley, Bowles and Mettler.
Reference 24 *reads:* Hemwich; *should read:* Himwich.

Page 153—Reference:
Reference 47 *should read:* Piotrowski, Z.: (*a*) Psychsom. Med., **1**, 508, 1939; (*b*) Psychiat. Quart., **15**, 807, 1941, etc.

psychomotor processes. Both drugs pave the way for more effective psychotherapy."

Young and Young[67] see a certain danger in allowing our interest to become too diffuse in the search for some answer to the schizophrenic problem when they say the ". . . . use of these methods carries the danger of arousing special interests along associated biochemical, physiologic, and neuro-anatomic lines. While such studies are necessary and informative, one should attempt to understand the changes of functioning of a part in terms of the integrative relationship of all the parts. There is also the danger of disregarding former disciplines and replacing them with a set of facts based on new methods of treatment. We feel that, no matter how striking the results of any special method, treatment of psychiatric disorders must continue along broad lines which focus the interest of the physician on the patient as a psychobiologic unit with complex sets of integration, functioning in a variety of life situations, past, present, and future."

Technique of Administration and General Management. The technique and general management of the shock therapies have varied a great deal since the original description outlined by Sakel and Meduna. The majority of authors outline their general procedures and stress any variation from the original methodology and phenomenology of these therapies. Variations on an original method seems to be one of the ways in which we try to progress in medicine, and a number of papers testify to this fact.

In the field of insulin therapy the following variations have been observed: 1, Protamine zinc insulin has been used by many workers who are in agreement with the conclusions drawn by Reese and Vander Veer,[50] "Protamine zinc insulin is not suited to hypoglycemic shock therapy for schizophrenia because (*a*) the effects of equal doses are not always the same; (*b*) the dose must be constantly varied, since no uniform shock dose can be established; (*c*) closer laboratory coöperation, with frequent determinations of the blood sugar, is required with this compound than with regular insulin; (*d*) the danger of after-shock is greater; and (*e*) epileptiform shocks are somewhat more frequent. Shock therapy with protamine zinc insulin differs from that with regular insulin, since (*a*) with large doses the fasting (morning) sugar level declines steadily, and (*b*) it is almost impossible to produce comatose wet shock."

2. The usual intramuscular route has been replaced by the intravenous route in some clinics with the following results: Jones[31] reports that coma is produced more quickly; however, same amount of insulin is required by the intravenous as by the intramuscular route.

Sherman, Mergener and Low[57] compared the effects of coma doses of insulin administered intravenously and subcutaneously to psychotic patients and found the following: "In a group of 13 schizophrenic patients the blood sugar fell more promptly in response to coma doses of amorphous insulin given intravenously than to those given subcutaneously. The fall in blood sugar in response to coma doses of insulin given intravenously occurs at about the same rate as in response to small doses, *e. g.*, 10 units. In the latter case the blood sugar returns to normal values rapidly, whereas in the former it stays low for a prolonged time, so that coma ensues. The only practical advantage of

the intravenous administration of insulin is the shortening of the precoma period. There was no appreciable difference in the coma doses required between the two methods of administration. There was no significant difference in the complications resulting from the two methods of injection. Spontaneous emergence from coma produced by intravenous insulin is rare."

Polatin, Spotnitz and Wiesel[48a] set out to produce insulin coma as quickly as possible and with a minimum of coma. They chose the intravenous route of administration and found that 48% of patients treated 2 weeks or longer showed improvement. They felt this route of administration had numerous advantages over the usual hypoglycemic shock technique. The shock period was shortened; patients recovered spontaneously from the shock to drink the dextrose solution; none of the patients had convulsions or received any detectable injury; the total amount of insulin per patient was less than that required subcutaneously to produce coma; a minimum of nursing supervision was necessary.

Polatin, Spotnitz and Wiesel[48b] extended the uses of intravenous insulin to ambulatory patients with mental disease. In a group of 18 patients they found that mild hypoglycemic shocks were of considerable value. They reported that in "81% of the patients so treated there was definite improvement. The beneficial effects are slowly cumulative. It was also observed that in some cases of dementia præcox this therapy is necessary over an indefinite period of time in order to maintain such patients on some level of social adjustment. This form of therapy warrants further investigation as to its effects upon the disorders of the central nervous system."

3. An interesting use of insulin has been the administration of subshock doses to schizophrenic patients. Bennett and Miller[5] found that subshock doses of insulin were of value in controlling most of the problems of management of uncoöperative patients, and corrected difficult feeding problems. They did not consider this therapy curative, although in their series many favorable remissions did occur. In addition to the papers already mentioned, other papers have dealt with interesting phases of insulin technique. For instance, McGregor and Sandison[40] report the use of potatoes used in connection with sugar in the interruption of the coma. They, too, report the intravenous route of administration with an average saving of 46.6% of insulin.

Hunt and Feldman[28] have pointed out that more rapid absorption appears to take place if the sugar solution is well-diluted and warmed before tubing the patient to terminate the insulin shock.

4. The most interesting variation in the administration of both metrazol and electric shock has been the introduction of curare by Bennett.[3a,b,4] The introduction of this drug made it possible to continue the use of metrazol and electric shock without the danger of inducing the fractures so prone to occur in these treatments. Bennett has also used scopolamine in the convulsive therapies and reports: "Intocostrin (standardized curare) is a valuable adjunct to convulsive therapy in that it removes the danger of fractures, particularly the vertebral type, sprains, backaches, and other unpleasant complications which have occurred in this type of treatment. It makes it possible to apply the therapy to mental cases who would be deprived of it because of some skeletal defect. Scopolamine is effective in reducing appre-

hension and post-convulsive restlessness in patients receiving convulsive therapy, particularly in those who have had no previous fear reactions. The combined effect of scopolamine and curare has been found almost completely to eliminate post-convulsive excitement."

Complications. The complications of the shock therapies have presented many problems, some of which have been solved, and others which have not been adequately explained. Probably the most serious complication of these therapies has been the injury to the skeletal system. Polatin, Friedman, Harris and Horwitz[49a] reported that of 173 patients treated with hypoglycemic shock therapy, 62 (36%) manifested epileptoid convulsions. Of these patients who were available for roentgenographic examination, 34 (20.5%) revealed compression fractures of the vertebræ. The same authors reported[49b] an incidence of 43.1% compression fractures in 51 cases treated with metrazol therapy. Along with the compression fractures of the vertebral bodies, fractures and dislocations of other bones have occurred. Femur, humerus and scapula have been fractured, while jaws and shoulders have been dislocated. The technique of administration has been altered in an effort to lessen the incidence of fractures. Curare has been very effective in preventing fractures; however, in our own clinic compression fractures of the vertebræ have occurred in 2 cases prepared for electric shock therapy by curare.

In addition to the use of curare as a means of protecting the skeletal system, other devices such as braces, casts, or specially designed beds to insure adequate hyperextension have been introduced.

The prolonged hypoglycemia, seen in most clinics treating patients with insulin shock, is probably the second most frequent complication. Some workers have suggested that protracted shocks should be induced for therapeutic reasons; however, Kant[32] cautions against such a procedure since he feels that in protracted shock there lies a danger of permanent organic brain damage. Lester[35] studied a series of cases suffering from a prolonged insulin coma and reported a mortality rate of 16%. He urged the avoidance of such a complication, and concluded that such a complication was not followed by improvement. Although a few dramatic improvements have occurred, prolonged coma should not be induced. Cleckley and Templeton[12] have witnessed prolonged non-hypoglycemic coma in 6 cases which failed to respond to extensive treatment with thiamin bichloride, nicotinic acid and riboflavin. Two of the cases came to autopsy; however, no adequate cause was found for the failure to awaken. Since prolonged coma is an unpredictable and dangerous complication, they advise the routine administration of protamine to all patients who develop this complication. Likewise they suggest riboflavin, nicotinic acid and thiamin chloride be used prophylactically in all cases undergoing treatment. The clinical signs seen in cases of prolonged coma have been explained by Binzley and Anderson[6] on a basis of actual cellular pathology. They consider the process to be an encephalopathy caused by interference with normal oxidation processes. Frostig[19] feels that the protracted shock occurs only in cases where the medullary phase was allowed to develop and persist for some time. In explaining this phenomenon, Frostig first places emphasis on the disturbed function of the medullary

nuclei, and second he feels that the continued carbohydrate deprivation of the control cells is a factor.

Epileptiform seizures frequently occur as a complication in the course of insulin shock therapy. Goldman[21] analyzed 3119 periods of hypoglycemic shock and found that the convulsion in hypoglycemia is a characteristic of individuals and not the method. Individual susceptibility varies greatly. Therapeutic benefits from this type of convulsion are questionable; however, cases have been seen to improve following a convulsion during hypoglycemia coma. Finiefs[16] reports such a series of cases in which convulsions occurred either spontaneously or were induced by metrazol. He felt that the occurrence of convulsions during the actual coma enhanced the value of the therapy. This is not the general consensus at the present time. Laryngeal spasm,[20] subarachnoid hemorrhage,[17] cerebral insult,[34] status epilepticus[20] and anaphylactic response[25] have been mentioned as further isolated complications of insulin therapy. Likewise, pulmonary edema, cardiac collapse, and changes in the control nervous system have been stressed by O'Neil[45] who observes that considering the amount of insulin administered, and the repetition of the treatment, it is remarkable that complications have not been more frequent.

The death rate from shock therapies shows a low incidence of 23 per 10,000 patients treated with insulin, and 23 per 10,000 patients treated with metrazol as cited by Kinsey.[33]

Considerable experimental animal work has been performed in an effort to ascertain the effect of the shock therapies on the central nervous system. Arieti[1] reported on 5 monkeys after metrazol-induced convulsions that the changes were not always proportional to the number of convulsions. Pathologic changes when found consisted of small groups of cells which presented acute degenerative changes, or, in some cases, the severe type of degeneration described by Nissl. In 2 cases anemia of the external cortical layers, anemic and hyperemic foci in the inner areas and generalized breaking up of the network of capillary blood columns were observed. These changes were considered functional and not responsible for the cellular lesions.

Cleckley, Bowles and Mettler[11] observed more striking changes in animals treated with metrazol. The lesions noted consistently appeared to be secondary to vascular constriction or vascular changes. No direct relationship existed between the degree of neuropathologic change and the total amount of metrazol; however, the degree and extensiveness of the lesions corresponded in general to the number and severity of the seizures.

Neubuerger, Whitehead, Rutledge and Ebaugh[42] induced electrical convulsions in 12 mongrel dogs. The findings were less severe than the changes found following metrazol injections. In the latter, the most important lesion is in the cerebral cortex. More or less complete necrosis of the nervous parenchyma was observed in small circumscribed areas.

Not all the deaths resulting from these therapies have been studied histologically, but sufficient numbers have been studied to give a glimpse of what happens to the brain. Weil and Liebert[64] studied 6 patients treated with metrazol injections and found the outstanding histopathologic features to be marked hypertrophy and hyperplasia of

astrocytes and, to a lesser degree, of the microglia. Involvement of the ganglion cells was less pronounced, although in 1 case of involutional melancholia there was generalized severe degeneration of the neuron with neuronophagia. These changes show a striking similarity to the changes found in experimental animals.

Jansen and Waaler[29] reported pathologic changes in 6 schizophrenics and 1 depressive who had been treated with insulin. In 3 of the cases the cause of death was considered cerebral in nature. In 1 of these cases the brain changes consisted of ischemic alterations in the cortex, diffuse proliferation of glia and slight vascular changes. In the other 2 cases, the changes included more extensive ischemic necrosis of the cortex in the frontal and temporal lobes, partly with hemorrhagic infarction. In the other 4 cases, there were only isolated subarachnoid perivascular effusions of blood and hyperemia.

Ebaugh, Barnacle and Neubuerger[14] report 2 deaths resulting from electric shock. In the first case, a man 59 years old suffering from a depression, the cause of death was due to coronary occlusion and myocardial infarction. In the second case, a man 52 years old, and suffering from a manic reaction, the general autopsy findings were negative. It was assumed the total outcome was due to postconvulsive respiratory arrest. Both cases showed rather widespread, but not serious, histologic changes in the brain.

Electrocardiographic and Electroencephalographic Findings. Closely allied to the complications frequently observed in shock therapies are the changes seen in the electrocardiogram and the electroencephalogram. Bellett, Freed and Dyer[2] took tracings on 40 patients during 58 shock treatments, and noted changes in two-thirds of the cases. These changes consisted of depression of the ST segment, diminution of the height of the T wave, prolongation of the QT interval, auricular fibrillation, auricular extrasystoles, shifting forewaters, sinus arrhythmia and sino-auricular heart block.

Messinger[41] reports that the most frequent electrocardiographic abnormalities in hypoglycemia are seen to be flattening and inversion of T waves and sinus arrhythmias. Other changes which have been noted are pathologic "q" waves, changes in R and S voltage, slight widening of the QRS complexes, appearance of "V" waves, appearance of auricular and ventricular extrasystoles. Goodrich and Smith[22] believe that the most frequent electrocardiographic change associated with prolonged insulin hypoglycemia is a lengthening of electrical systole. They further state that important electrocardiographic changes do not occur during severe hypoglycemic coma, nor does repeated hypoglycemia produce any persisting changes in the electrocardiogram. Sonenthal and Low[58] are in agreement with these statements and go further in stating that electrocardiographic records following investigations of metrazol and insulin treated patients reveal no evidence of myocardial damage months after termination. Electrocardiographic studies were made on 50 schizophrenic patients treated with metrazol by Levine, Piltz and Reznikoff.[36] One hundred electrocardiograms were taken, 50 before and 50 after treatment. In only 2 patients were the changes considered significant and in each case they were believed to be transient.

Measurement of brain potential during insulin hypoglycemia has

been reported by Hoagland, Rubin and Cameron.[26] In a series of 35 tracings taken on 6 patients during insulin shock they report a progressive decline in alpha-wave-frequency of some 40%, which parallels with a time lag of some minutes the declining blood sugar curves. Sugar injected during coma restores the frequency along a smooth curve. The alpha-frequencies are believed to be directly proportional to the rate of carbohydrate metabolism of the cortical cells producing the rhythm. It is interesting that the same authors,[27] reporting later on the "Delta Index," stated that in the schizophrenic patients treated with hypoglycemic shock they have found no special brain curves qualitatively different from those found in normal persons.

Modus Operandi. Perhaps the most fascinating question raised by the shock therapies is the manner in which improvement occurs or the *modus operandi* of the shock therapies. No one has hit upon an explanation which has met with the approval of the majority, but certain theories have appeared and reappeared which warrant our attention.

The fundamental physiologic mechanisms involved in shock treatment are unknown, but the diminution or suspension of brain metabolism during treatment seems significant.[65b] Freudenberg[18] states that, "Although the metabolic findings in schizophrenia are not absolutely specific, the following hypotheses concerning its basis and the mechanism of cure can be regarded as established. In schizophrenia there is probably a primary disturbance in cerebral respiration, perhaps due to some lack of oxygenating substances. This disturbance leads to a collection of toxic products, probably originating from the protein metabolism. Insulin therapy induces the oxybiotic processes necessary for detoxication and also an irritation of the cell membranes, which results in an increased exchange between the cells and their surroundings. Similar but more sudden changes take place in cardiazol therapy."

On the basis of observations of clinical symptoms, cerebral oxygen utilization, blood sugar level and electrical activity of the brain, Himwich, Frostig, Fazekas and Hadidian[24] were able to conclude that as a result of the hypoglycemia caused by the administration of insulin, the metabolism of the brain is diminished.

Spiegel and Spiegel-Adolf[59] attempt to explain the convulsions in metrazol and insulin therapy due to an increase in the permeability of the cellular surface films. This increase facilitates the exchange of ions between the cytoplasm and its environment and the removal of products of its metabolism.

Many are not satisfied with even this partial explanation on a physiologic or organic basis, and they therefore propose a theory on a psychologic basis. Improvement is considered due to the patient's experience of the treatment as a threat to his existence, or as punishment, or as death and rebirth.

Jessner and Ryan[30b] feel that hypoglycemia changes the organism in such a way that the patient becomes able to turn his affection and his interest to persons and objects of the outside world and so to give up his narcissistic isolation. Whether this altered attitude is merely temporary or becomes permanent depends greatly upon his capacity to endure reality, with its alluring and threatening qualities.

The status of our understanding of the *modus operandi* is best summarized by Müller's[42] statement, "Neither the endocrine phase of the

treatment nor brain pathology, nor the question of convulsions, nor the soothing, quieting effect, nor failing consciousness, nor the potent psychic shock . . . . is alone sufficient to solve our problem."

Psychologic Factors. Various psychologic tests[7,46,63] have been used to determine the changes which take place during treatment, and on the whole these tests tend to indicate what benefits may be expected of the treatment. The Goodenough test[15] has shown that some patients have been harmed by the therapy instead of helped.

The Rorschach test has been used to show improvement following therapy,[23,47a] to predict the outcome of therapy, and as a prognostic guide.[47b,c] Piotrowski[47d] claims that if only those patients who show that color has meaning for them were treated, the percentage of improvements would be increased.

Follow-up Studies and Prognostic Factors. Coupled with the Rorschach test, good clinical practice and observation are of great value in predicting the outcome of the schizophrenics treated with insulin. According to Cheney and Clow[10] the dementia præcox patient who has the best outlook for recovery or improvement following insulin therapy is a male under the age of 30 who has had a comparatively adequate prepsychotic personality, whose psychosis had an abrupt onset with a definite external precipitating cause. He will have been sick less than a year before the institution of treatment; he will have shown an excited catatonic state without evidence of what we have called deterioration, which is defined as consistent lack of attention to personal habits, bizarre behavior, disconnected thinking, and apathy. Conversely, the patient not likely to benefit by hypoglycemic treatment will be a female over 30 who, with an inadequate personality, insidiously and without definite external precipitating cause, has developed over a period of more than a year before treatment a mixed form of dementia præcox with evidence of deterioration as defined above. Of great significance is Cheney's remark that patients who will benefit by insulin treatment will have the same characteristics as those benefited formerly with other forms of treatment. This supports our conviction that insulin does not have a specific curative effect, but that it may bring about changes that accelerate or facilitate improvement in those who have the constitutional capacity for such improvement or recovery.

Wall[62] found in a study of 37 schizophrenics that those cases which showed typical schizophrenia, presence of considerable emotional reaction, a history of some attempt at sexual adaptation, and manifestation of sexual interest in the psychotic state would be benefited by insulin shock treatment; whereas those patients who reacted poorly to the treatment showed the following factors: "Very frequently came from a poorly integrated family with little solidarity among its members. In many instances as children they were considered in some respect different from the other siblings. They adapted to school in a somewhat worse than average fashion and showed a lack of ambition. They showed very little sexual interest prior to the psychosis and there were no overt sexual manifestations other than autoeroticism during the psychosis. Almost all of the patients who exhibited autistic behavior (mannerisms, grimacing, posturing, etc.) failed to respond. They showed a picture of typical schizophrenia without extraneous admixtures."

Rymer and Ebaugh[55] noted that follow-up reports on the shock therapies are relatively scarce, and the majority of these are reported for only short periods, although many workers warn against interpreting results based on too brief study. Malzberg,[39] in a series of 1039 schizophrenics in the New York State Hospital set-up, found that the number of patients who had been reported as "recovered" at the termination of their insulin therapy remained constant at the end of the first year, but that the percentage "improved" dropped from 65.4% to 49% during this period. However, this represented a significant improvement over patients with schizophrenia who did not receive insulin shock therapy. In a later article, he and his coworkers, Ross, Rossman, Clive and Schwoerer,[53] report that records and results are so poorly standardized that little can be concluded as to the real efficiency of insulin therapy, and they urge the establishment of "uniform criteria for the interpretation of the results of treatment."

Ruslander[54] in a series of 55 cases treated with insulin found that 44% of the cases were sufficiently well to be discharged at the expiration of 1 year's parole. He noted a lack of improvement in patients ill longer than 18 months. Robinson[51] reports 90% "excellent results" in 13 patients 18 months after treatment. Bond[8] followed a group of 125 patients for 2 years and found that while one-half of all patients treated showed improvement at the termination of treatment, one-half of these had relapsed by the end of the second year. Somewhat better results were obtained in cases with an acute onset: two-thirds of these showed improvement, although one-half had relapsed at the end of the second year. Rymer and Ebaugh[55] in reporting the follow-up of 400 cases treated with shock therapies draw no conclusions as to the superiority of this type of treatment over that of careful non-shock therapy, but believe that the work is still experimental and requires intensive study on comparable groups over long periods.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF MAY 19, 1942

Acetate and Intestinal Motility. J. F. McClendon, John Scott, W. C. Foster and Morton J. Oppenheimer (Laboratories of Physiology, Hahnemann Medical College and Temple University School of Medicine). The senior author[1] suggested that the laxative action of "roughage" is due to carbohydrate fermentation (acetate). In testing this hypothesis we found that we could increase the weight of the feces of a rat 10% by feeding acetate but 1000% by feeding agar or

[1] McClendon: J. Biol. Chem., **87** (Proc. XXIV, vii), 1930.

alginic acid (although these are to a large extent broken down by fermentation in the gut and the bulk of the feces cannot be ascribed to unaltered "roughage"). The difference is probably due to the fact that acetate fed as such is totally absorbed in the proximal part of the intestine whereas the acetate arising from fermentation of "roughage" is continually produced through the whole length of the intestine. Balloons were introduced at various levels into gut of trained or anesthetized dogs or rabbits and acetate introduced in the region of the balloon or elsewhere. The frequency of contractions remained constant but they varied in amplitude. The pH of the acetate did not seem to make a difference. The moderate pressure in the balloon was itself a stimulus to increased amplitude and was kept as constant as possible during an experiment. When the acetate reached the region of the balloon a greater effect on amplitude was obtained than when the balloon was in a Thiry-Vella fistula to which the acetate had no access. Even when the balloon pressure was minute or negative (Biebl exteriorized gut) the acetate increased the amplitude. Sixty cc. of N sodium acetate given by stomach tube to a fasted dog caused it to defecate in 25 minutes and 100 cc. caused another to vomit in 12 minutes.

Studies in Serum Protein Fractionation by Salt Precipitation in Infants and Children. MILTON RAPOPORT, MITCHELL I. RUBIN, and DORCAS CHAFFEE (The Children's Hospital of Philadelphia and the Department of Pediatrics, University of Pennsylvania School of Medicine). Plasma proteins of healthy and diseased infants and children were determined, using both the Howe technique and the phosphate precipitant of Butler and Montgomery. Fibrin was also determined.

Blood fibrin in healthy children was constant at all age levels studied, having the same value in premature infants as in older children. Total protein increased progressively with age, as did albumin and globulin. The albumin value attained the adult level in early infancy (2 months), but the globulin values were still significantly low at 11 months of age. There was a constant reduction of a globulin fraction precipitating between 1.2 and 1.6 molar concentration of the phosphate precipitant, through the entire period of infancy.

In *glomerulonephritis*, blood fibrin is elevated at all stages of the disease. In chronic glomerulonephritis there is reduction of the globulin and albumin, and also of a globulin fraction precipitating between 1.2 and 1.6 molar concentration of phosphate precipitant; this same fraction is increased in acute glomerulonephritis, returning to normal with complete recovery from the disease.

In the *nephrotic syndrome*, plasma fibrin is increased and serum albumin markedly reduced. Even though globulin was normal by the Howe technique, a reduction in the globulin fraction precipitating between 1.2 and 1.6 molar phosphate precipitant was found.

Reproduction and Lactation of Mice on Highly Purified Diets. CLAIRE FOSTER, JAMES H. JONES, FRIEDA DORFMAN and RUTH S. KOBLER (Departments of Pediatrics and Physiological Chemistry,

University of Pennsylvania School of Medicine). Mice have been raised to the fourth generations of offspring on a basal diet composed of purified fibrin 25%, salt mixture 4%, regenerated cellulose 4%, and glucose 67% with the following supplements added to 100 gm. of the basal diet in the amounts indicated: Linoleic acid 2 ml., alpha-tocopherol 6 mg., crystalline vitamin A 100 γ, naphthoquinone 5 γ, calciferol 2.5 γ, thiamine hydrochloride 1 mg., riboflavin 1 mg., pyridoxine hydrochloride 1 mg., calcium pantothenate 6 mg., nicotinic acid 6 mg., inosital 6 mg., para-aminobenzoic acid 15 mg., and choline chloride 60 mg. Fertility as determined by litters born per females mated and by size of litters was about equal to that of animals on a good stock diet but growth and survival to weaning were definitely below normal. The subnormal growth became more noticeable as the number of generations increased until in the F_3 generation the young were so small at the weaning age of 21 days that many of them removed from their mothers at that time died. Two females of the F_3 generation were mated and gave birth to 15 young of which only 2 survived to weaning. In all 73 females were mated and 63 litters were born totalling 447 young. Of these, 272 (61%) were weaned. This compares with the weaning of about 85% on our regular stock diet. Whether the ultimate failure depends upon an insufficient amount or an imbalance of the presently recognized factors or the absence of an unknown factor remains to be determined.

The Relation Between Oxygen Consumption and Cardiac Output in the Presence and in the Absence of Cardiac Disease. ISAAC STARR and LEON JONAS (Hartzell Department of Research Therapeutics and William Pepper Medical Laboratory, University of Pennsylvania). The change in the amount of the circulation for a given change in O_2 consumption has long been of interest.

Assembling the experiments of numerous investigators in which O_2 consumption was increased by exercise, Boothby and Rynearson drew a straight line through the data. This line was not a calculated regression; it indicated that when the O_2 consumption doubled the circulation increased by about 60%.

This relation has also been investigated in hyperthyroidism. For a doubled oxygen consumption Liljestrand and Stenstrom found the circulation to increase about 120%; Fullerton and Harrop about 138%; and Boothby and Rynearson about 72% on the average. Combining the data of the last two papers the line drawn by Boothby indicates approximately a 1 to 1 relationship between increases in circulations and O_2 consumption.

All these data may be criticized, for as the value for the O_2 consumption was a factor in the authors' estimate of the circulation in the cardiac output methods employed, so O_2 consumption and circulation (as calculated) were not independent variables and the relation between them was forced.

We have data in 32 cases of thyroid disease without cardiac complications in which the estimations of O_2 consumption and cardiac output were completely independent. The calculated regression of these data

passes almost exactly through the origin and its slope is close to unity. The correlation coefficient is 0.84, any value over 0.28 being significant.

We also have similar data for 28 cases of advanced heart disease. This regression passes below the origin and its slope is close to 0.5. The correlation coefficient is 0.69, any value over 0.32 being significant.

We conclude that, if the heart is normal, changes of metabolic rate in thyroid disease are accompanied by similar percentage changes in the circulation, a conclusion not far from the average result of our predecessors. In heart disease changes of metabolic rate are accompanied by changes in the circulation about one-half as great.

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this Journal to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of "milligrams per cent"—is well covered on Page 53 of the American Medical Association's book entitled "Medical Writing": "Results of chemical determinations are frequently expressed as 'milligrams per cent' or 'grams per cent.' This means literally 'milligrams (or grams) per hundred milligrams (or grams),' which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as 'milligrams per hundred cubic centimeters' or 'milligrams per 100 gm.' If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply 'per hundred cubic centimeters' the first time the phrase appears and to use merely 'milligrams' (not 'milligrams per cent') thereafter." We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the Journal of the American Medical Association with its large circulation, will also emphasize the point.

We would like to regard the word "consider" as indicating that the item is still under consideration or being meditated upon, *i.e.*, that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as "think to be," or "regard as" or "believe to be" or "hold as an opinion" give the more exact meaning.

THE EDITOR.